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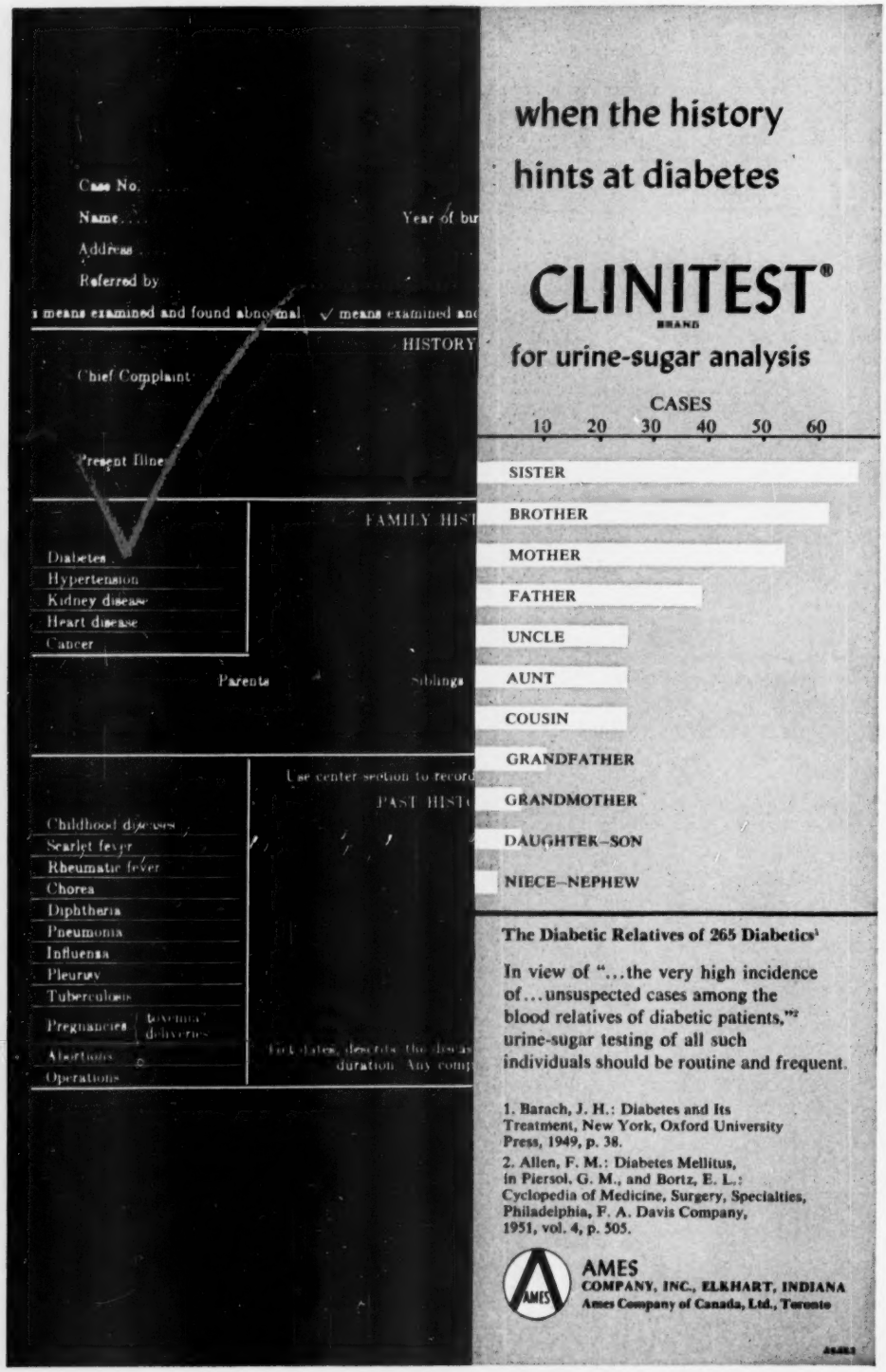
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1. Barach, J. H.: Diabetes and Its Treatment, New York, Oxford University Press, 1949, p. 38.
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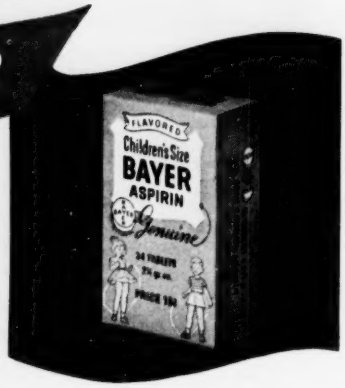

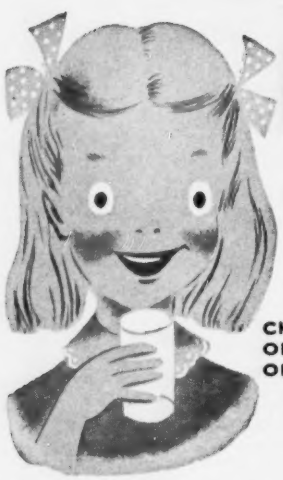

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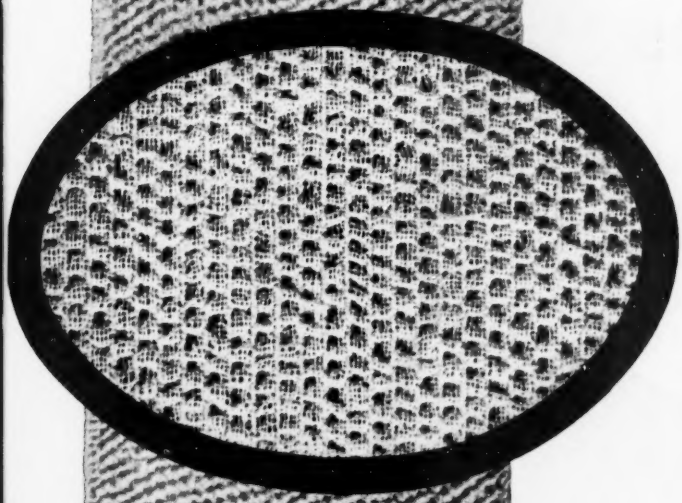

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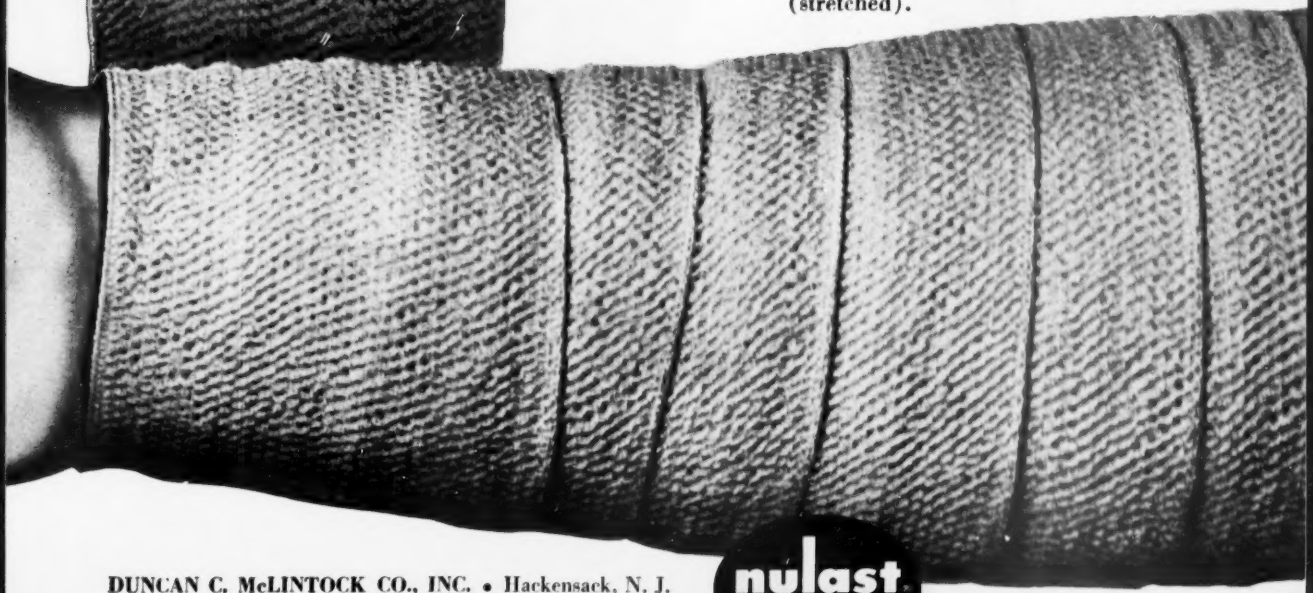

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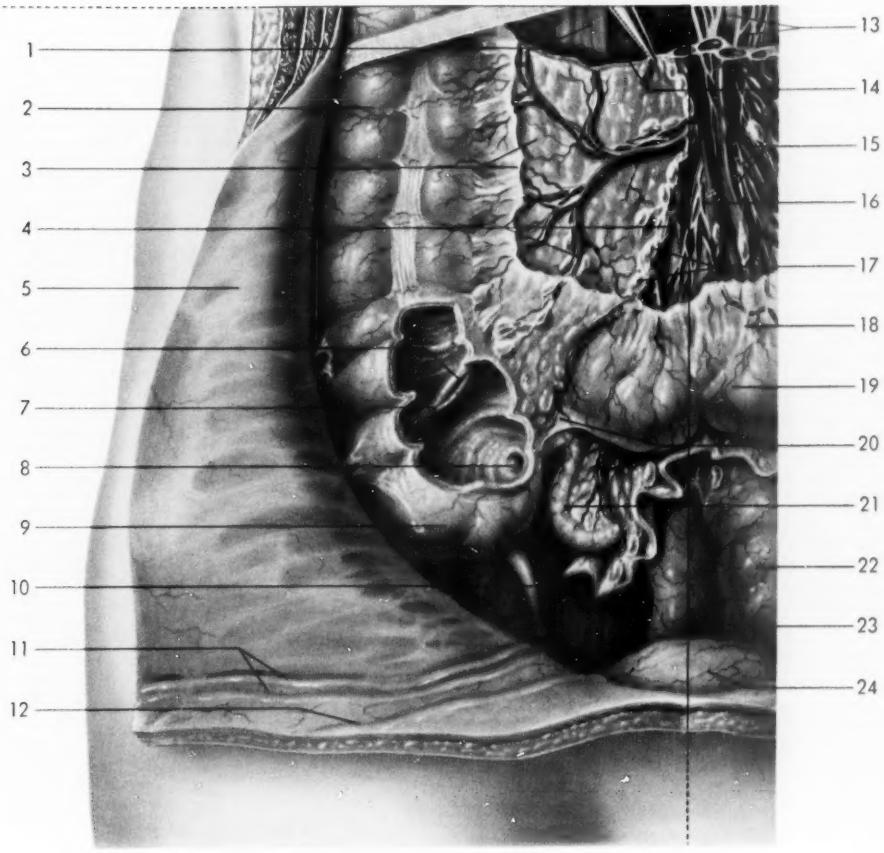

1 Spermatic artery and vein
2 Ascending colon
3 Mesocolon
4 Branches of ileocolic artery and vein
5 Parietal peritoneum
6 Ileocecal valve
7 Frenum
8 Appendicocecal valve
9 Cecum
10 Ureter and external iliac artery and vein
11 Epigastric artery and vein
12 Lateral umbilical ligament
13 Aorta and abdominal aortic plexus
14 Vena cava
15 Intestinal arteries and veins
16 Sympathetic abdominal plexus
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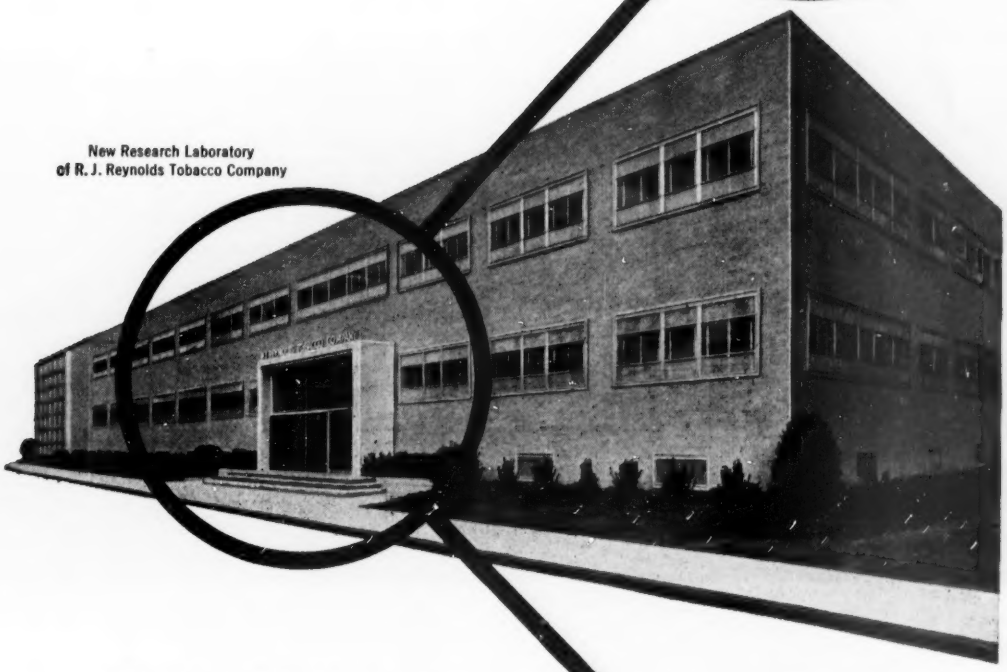

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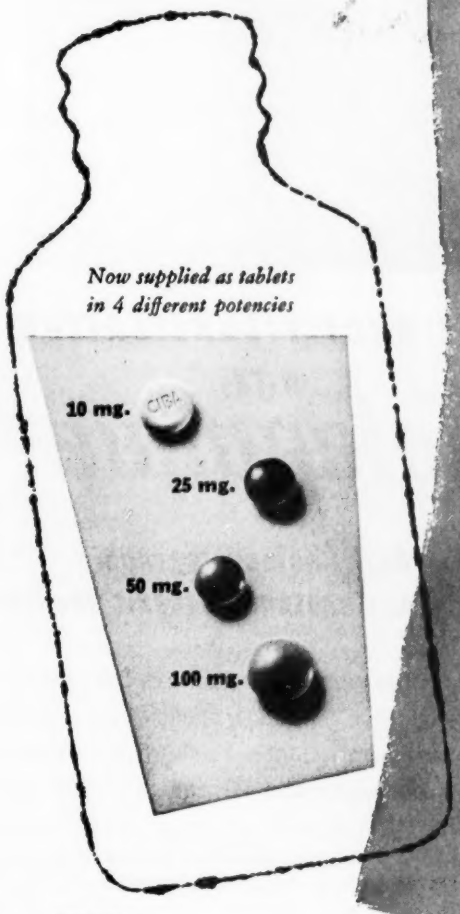

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SOME SURGICAL PROBLEMS PECULIAR TO THE TROPICS*

BEN EISEMAN, M.D.†

ST. LOUIS, MISSOURI

THOSE who spend a large part of their professional lives practicing surgery in temperate zones and in areas where the standard of living and nutrition is relatively high are often unaware of the many problems foreign to their experience that are encountered in the practice of surgery in the tropics. In a world where rapid transportation continually increases interdependence with formerly remote areas it is interesting and perhaps profitable to overcome this surgical isolationism and to review some of the problems that confront surgeons in a tropical area such as Southeast Asia.‡ A great deal has been written about tropical disease and comparative geographic pathology, but surprisingly little on the surgical aspects of such problems.

NUTRITION AND VITAMIN DEFICIENCIES

A lack of thiamine is the most common single vitamin deficiency in Southeast Asia, owing to the usual basic diet of polished rice, which lacks vitamin B_1. Frank beriberi is a common disease but does not fall strictly within the realm of a surgical problem. However, the patient awaiting surgery is often suffering from a subclinical thiamine deficiency that becomes manifest as frank beriberi after an operation or parturition.

Soreness and tenderness in the calf of the leg is one of the early signs of thiamine deficiency. Appearing as it does on the third or fourth postoperative or post-partum day, a clinical picture is presented that is difficult to differentiate from early thrombophlebitis. Homans' sign is positive; there may be swelling of the leg, and there is exquisite tenderness in the calf. A therapeutic trial of large doses of thiamine will usually terminate the peripheral symptoms and signs of beriberi within a few days.[1]

Malnutrition of various degrees and hypoproteinemia are common in tropical areas, but the surgeon accustomed to the relatively overnourished and obese patient in the United States often underestimates the reserve and durability of the thin, wiry patients frequently encountered in tropical practice. Surgeons with experience in the tropics realize that these patients tolerate major surgical procedures well, and they will undertake surgery on a thin person whom a newly arrived surgical colleague from the temperate zone would consider to be in a state of hopeless malnutrition.

POSTOPERATIVE PYREXIA

Frequently, in the tropics, postoperative malarial pyrexia occurs. Relapses of chronic malaria are readily caused by anesthesia or operation. A postoperative relapse may begin insidiously from the third to the tenth postoperative day or may explode dramatically, with classic fever and chills within forty-eight hours of the operation.

In the medical centers of Southeast Asia as elsewhere in the tropics, the transfusion of blood is being practiced more frequently in the preparation and care of the surgical patient. In areas where malaria is endemic most of the donors have been infected, and most of the banked blood harbors malaria parasites. It has been assumed that holding refrigerated banked blood for forty-eight hours destroys both the treponema of syphilis and the plasmodium of malaria, but there is no experimental proof of the hypothesis. Actually, post-transfusion malaria is so frequent that a prophylactic course of antimalaria therapy is given routinely after the transfusion of blood.

CARDIORESPIRATORY STATUS OF THE SURGICAL PATIENT

A preoperative cardiac and respiratory evaluation of the patient must necessarily include a recognition of the peculiarities of these problems as encountered in the tropics. Coronary-artery disease, arteriosclerotic cardiovascular disease and hypertension are much less common than in temperate zones, probably owing in part to the short average life expectancy and the rarity of obesity among the population.

Pulmonary disease is a frequent complicating factor in the evaluation of the surgical patient in the tropics. Although bronchiectasis is relatively rare, active tuberculosis is so frequent that the surgeon

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†Associate professor of surgery, University of Colorado School of Medicine, Denver; formerly, assistant professor of surgery, Washington University School of Medicine, and assistant surgeon, Barnes Hospital and St. Louis Children's Hospital.

‡The clinical background for these remarks consisted primarily of intermittent surgical experience over a three-year period as a member of the Washington University Medical School Affiliation Program in Bangkok, Thailand.

must revise his conception of pulmonary tuberculosis as an incidental finding before operation. To refuse to perform a needed operation on the grounds of pulmonary tuberculosis would be to deny many patients the benefit of operation, and the surgeon must in most cases compare the possible benefits of surgery with the danger of activating or spreading the tuberculous infection. The high incidence of pulmonary tuberculosis often predictates the type of anesthesia employed.

Urinary-Tract Calculi

Statistics may be unreliable in some areas of Southeast Asia, but even the most casual medical observer is impressed by the high incidence of urinary-bladder calculosis. One need only inspect the mounds of bladder calculi collected in the provincial hospitals in many parts of Thailand to appreciate the frequency of this condition. In many such hospitals gravel and stone heaps each a foot or two high are collected within a few years' time. Children of a few months of age, as well as old men of seventy, suffer from this condition. Cystotomies for removal of bladder calculi far outnumber any one other single operative procedure in many provincial hospitals in Thailand. Most of the inhabitants of these districts are well aware of the symptoms of vesical calculi and frequently report to the hospital volunteering the information that they have a bladder stone, and request its surgical removal. After the rice has been harvested, the dry season has begun and work is less demanding, it is common in northeast Thailand to see a number of families camped outside the provincial hospitals waiting their turn for a hospital bed and a place on the operating schedule for cystotomy and removal of vesical calculi. The high incidence of bladder stone has been the subject of a good deal of investigation, particularly since the problem exists in many tropical countries.[2] Careful studies have proved that these calculi are not secondary to parasitic infestation of the bladder, as in Egypt, where *Schistosoma haematobium* is endemic; no such bladder parasites exist in Southeast Asia.

The relation between bladder stone and diminished urinary output consequent to a hot environment has been investigated, but there is no direct evidence that this factor is of etiologic significance. Other hotter and more arid countries do not have as high an incidence of bladder calculi.

There is good clinical and experimental evidence that vitamin A deficiency is an important cause in the formation of bladder stone in Southeast Asia. Experimentally, bladder stones are formed in a large percentage of young mice maintained on a diet deficient in vitamin A. Inhabitants of stone-forming districts in northeastern Thailand subsist largely on glutinous (sticky) rice and fish — a diet notably lacking in vitamin A. Other clinical signs of vitamin A deficiency are not evident among these people, but dark-adaptation studies and blood-vitamin determinations have not been reported. It is doubtful if vitamin A deficiency is the sole cause of urinary calculi since the inhabitants of northern China suffer from vitamin A deficiency but do not have a high incidence of vesical calculi.

An interesting by-product of the high incidence of bladder stone in many areas in the tropics is its salutary effect on the attitude of the people toward surgery and the acceptance of operation when so advised. In such districts almost everyone has an acquaintance who has had a bladder stone removed, usually with gratifying relief and lasting benefit.

Obstetrics and Gynecology

Any surgeon or gynecologist working in Southeast Asia soon becomes aware of the high frequency of ectopic gestations among the population. At the Siriraj Hospital in Bangkok, a 550-bed general hospital, a patient with ruptured ectopic pregnancy is admitted almost daily, and this is one of the most frequent acute surgical conditions of the abdomen. It is thought that the high incidence of pelvic inflammatory disease with subsequent pelvic adhesions accounts for the high incidence of extrauterine pregnancy.

Chorionepithelioma is a rare tumor in most parts of the world, but for some obscure reason is frequently encountered in many parts of the tropics. Large numbers of deliveries are carried out without the aid of professional assistance, and it has been suggested that this accounts for the high incidence of retained placental fragments, which may degenerate into nonmalignant moles or chorionepitheliomas. Such a theory is difficult to substantiate.

Burns

The accepted treatment for severe burns in the tropics as elsewhere is the application of pressure dressings and early skin grafting. The vast quantities of bandage required for such a technic are difficult to obtain, and it is understandable that the open or exposure method has been extensively employed. Despite careful choice of burns suitable for exposure treatment, the results have been disappointing. The firm, dry coagulum that is the basis of such a method of treatment frequently fails to form in the moist heat of the tropics and exposed burns remain soft and macerated and often become infected. A more careful clinical experiment is required to determine whether the factor of atmospheric humidity is of major importance in the open treatment of burns, but clinical impression indicates that burned patients in a humid climate do not do well with the exposure method of therapy.

Opium Addiction

In most parts of the world opium addiction is rare, but in the Orient this is unfortunately a more common affliction. The surgeon must beware of

addicts, whose management is fraught with difficulties. Their complaints, both real and fancied, are legion, and they are usually poor surgical risks. Their nutritional status is poor, their mental attitude toward recovery abnormal, and their complaints, both objective and subjective, endless and acute.

Among the symptoms of opium addiction are gastrointestinal cramps, associated with severe abdominal pain. Such patients present a classic picture of small-bowel obstruction, with vomiting, obstipation, a distended abdomen and a ladder-like intestinal pattern that is clearly visible through the emaciated lax musculature of the thin, waxy looking abdominal wall. The bowel under such conditions has functional ileus in some segments, whereas adjoining sections have normal or even increased peristaltic activity. The surgeon must not confuse this functional ileus with mechanical obstruction requiring surgical interference, for soon after opium is administered to such patients the functional obstruction disappears, flatus is expelled and the distention is relieved.*

Postoperative nutrition in these patients is extremely difficult. They manifest no desire to eat and often vomit what is administered by gastric tube. Ambulation is difficult, and the problem of sedation fraught with complications because of their previous drug addiction. In general it is necessary to maintain their opium intake during the postoperative period to forestall withdrawal symptoms.

Neoplasms

A number of studies have been made concerning the relative incidence of tumors in various parts of the world.[3] That there is a true difference in incidence of neoplasm cannot be denied, but such variations are often considered more frequent than actually proves to be true upon more careful analysis. In many parts of the tropics data concerning the incidence of neoplasm are scanty and unreliable, and statistics derived from them are not valid and cannot be compared with those of other geographic areas. Trained surgeons and pathologists practicing in the tropics usually find approximately the same neoplasms as exist in temperate zones. The fact that the average life expectancy is low exerts a selection factor in interpreting the frequency of neoplastic disease. Although life expectancy is well under forty years in many parts of the tropics, infant mortality accounts for a large proportion of the deaths. There are therefore a large number of people who live on into their sixth and seventh decade and are subject to the usual neoplastic diseases.

Carcinoma of the lung is comparatively uncommon in Thailand. Dr. Frank Vellios, pathologist for the Washington University group in Thailand in 1951–52, reported only 1 primary carcinoma of the lung among 422 malignant tumors examined in the two medical-school hospitals in Bangkok.[4] This report included material from 198 autopsies. Many physicians in Southeast Asia who are well versed in the clinical, radiologic and laboratory appearance of lung cancer agree that carcinoma of the lung is relatively rare. It is noteworthy that cigarette smoking has for many years been a common habit among these people, tobacco being one of the main crops in parts of both Thailand and Burma.

The true incidence of carcinoma of the intestinal tract is not known for most parts of Southeast Asia, but the experienced clinician will find the usual number of cancers of the stomach, colon and rectum. Carcinoma of the esophagus, however, appears in relatively greater numbers, as in China.[5] It is interesting that these esophageal carcinomas appear to be more frequent among the Chinese living in Southeast Asia than among the Thai, Malayans or Indonesians in the same community. The frequency of this tumor among the Chinese has been somewhat arbitrarily attributed to the drinking of excessive amounts of scalding hot tea or to their highly spiced food. Neither of these food factors appears to be entirely different from those of the non-Chinese living in similar surroundings, who do not seem to suffer from such a high incidence of esophageal cancer.

Carcinoma of the lip and buccal mucosa is allegedly very common among those who chew betel nut,[6] a habit still practiced by a large number of the rural population and the older generation in Southeast Asia. True incidence of buccal-cavity carcinoma is difficult to determine, but most surgeons practicing in Southeast Asia do not believe that it is particularly high. Experience in India suggests that such cancers are related to the tobacco leaf mixed with the betel nut rather than to betel nut itself. Where tobacco is not included in the betel-nut quid buccal carcinoma apparently is less commonly encountered.

Both primary and metastatic tumors involving the cervical lymph nodes are common in most parts of the Orient. In north China and Formosa there is a high incidence of primary nasopharyngeal carcinoma, typically with a small inaccessible primary and more evident cervical metastasis.[7] In the tropical areas of the Orient a radiosensitive primary cervical tumor morphologically akin to a lymphoepithelioma is prevalent. Bonne[8] and other Dutch pathologists previously described this tumor and have classified it as a reticuloendothelioma.

Liver and Biliary-Tract Disease

Amebic hepatitis is often encountered in the tropics and must be differentiated from acute cholecystitis. When doubt exists about the cause of right-upper-quadrant pain, a therapeutic trial of

*An interesting give-away sign of the opium addict in the Orient is an area of baldness just behind the ears. This alopecia results from the habitual posture of the patrons of opium dens, where the smokers lie unmoved for hours with their heads crotched on concave wooden pillows that touch the head just behind the ears.

emetine or chloroquine is indicated. Amebic liver abscess, on the other hand, may appear gradually and must be differentiated from pericholecystic or other types of hepatic abscesses. If such an inflammatory mass is present, needle aspiration may be indicated, for if anchovy-sauce amebic-abscess fluid is obtained emetine or chloroquine therapy is usually extremely effective. These drugs can be instilled locally into the abscess cavity after aspiration of the pus.

Hepatic cirrhosis is a common finding in the Orient and in many parts of the tropics. *Clonorchis sinensis*, the parasite ingested in raw fish, is responsible for much of the cirrhosis in China, but is supposed to be almost nonexistent in Southeast Asia, where liver disease is extremely common.

Locally, many physicians believe that chronic malaria is the cause of the cirrhosis, but there does not seem to be any evidence to support this clinical impression. Lack of some dietary factor is much more likely to be the cause for such a high incidence of liver disease, which may be prominent in children of only a few months of age.[9]

Surgeons practicing where hepatic cirrhosis is so common must be particularly alert for anesthetic complications, a problem magnified by a scarcity of anesthesiologists and proper anesthetic equipment. In the districts where portal cirrhosis is so common one also finds a high incidence of primary carcinoma of the liver, a tumor related to cirrhosis but not necessarily associated with parasitic infestation. Surgical excision of such tumors is technically difficult, and the prognosis is poor, although more partial liver resections are now being attempted. The early clinical course of this neoplasm is often asymptomatic, and by the time laparotomy is performed the tumor has usually spread throughout all lobes of the liver.

Cholecystitis and cholelithiasis not only seem to be less common in the tropics than in temperate zones but also appear to be about evenly divided between men and women. Possibly, the rarity of cholesterol gallstones is related to the low average blood cholesterol level of the inhabitants of most tropical countries.

Extrahepatic biliary-tract obstruction is occasionally found in tropical practice owing to a matted mass of parasites plugging the common duct. This relatively rare complication of *C. sinensis* or *Ascaris lumbricoides* infection is seldom seriously considered until the common duct is explored and a mass of worms found packed in the dilated duct — an experience the surgeon does not easily forget.

Diseases Allegedly Rare in the Tropics

To state that a pathologic entity does not exist in a certain part of the world merely because it has not been reported or recognized is a common error. It appears, however, that some diseases common in the United States are almost unknown in Southeast Asia.

Hypertrophic pyloric stenosis is rarely found in Southeast Asia despite the fact that there are many well trained pediatricians in these countries who have seen infants with this condition while studying in Europe or in America. Until a year ago the only infant operated upon in Thailand for this condition was an American child living in Bangkok. There is no satisfactory explanation for the infrequency of this disease.

Erythroblastosis fetalis and other complications resulting from Rh incompatibility do not exist in the Orient owing to the fact that the inhabitants are almost without exception Rh negative.[10]

Duodenal Ulcer

It has been commonly accepted that duodenal ulcer does not exist among the unharassed inhabitants of Southeast Asia. Recently, an article in an American lay magazine, referring to one of these countries as the "land of smiles," reported that peptic ulcer was unknown among its happy inhabitants. Duodenal ulcer, however, does exist in Southeast Asia, and physicians practicing in that area are well aware of this fact. The relative incidence of peptic ulcer is difficult to determine, but it is certainly not low. In the region around Velore in southern India peptic ulcer is far more common than in the United States.[11]

The dietary management of duodenal ulcer is particularly difficult in the tropics since the commonly prepared foods are highly spiced and a bland diet is almost unheard of.

Religious dictates often make the dietary management of patients with ulcer even more difficult. Buddhist priests may eat only between the hours of 6 a.m. and 12 noon, fasting the rest of the day. The Moslems of Malaya and Indonesia, on the other hand, are required to fast throughout the entire daylight hours during certain religious festivals. It is understandable, therefore, that medical therapy of peptic ulcer is difficult and surgical interference is frequently required.

Surgical Complications of Parasitic Disease

A few of the parasitic infestations common in the tropics have complicating features that demand surgical attention.

The granulomatous masses resulting from amebic infection, referred to as amebomas, are more written about than seen. Such granulomas occur in the large bowel, but are considered somewhat of a clinical rarity even in the tropics.

Parasitic infestation by a spiny round worm, *Gnathostoma spinigerum* or *siamense*, is occasionally found as a larva migrans in some parts of Southeast Asia. These worms, harbored by dogs, cats, cattle, and swine, form in man a migrating series of subcutaneous swellings that usually break down and

produce low-grade abscesses. The lesions have been discovered in all parts of the body but are most frequently observed beneath the skin. The gross and microscopical pathology of this condition has been carefully described by Prommas and Daengsvang[12] and others from the Department of Pathology in the Siriraj Hospital and Medical School in Bangkok. The treatment of gnathostoma infection consists in surgical removal of the worms and sterilization or total excision of the abscess cavity.

The deforming sequelae of filaria infection are also common in many parts of the tropics, and their surgical correction is often attempted. Legs tremendously swollen and chronically infected after filariasis usually have skin and subcutaneous tissue so thickened by repeated bacterial infection that the classic Kondoleon procedure is usually valueless. Such fibrotic tissue must be totally excised, and the healthy muscle and deep fascia covered by large sheets of split-thickness skin grafts.

Intestinal parasitic infestation is common in the tropics and occasionally requires surgical attention. Hookworms cause anemia and blood in the stool that may simulate or obscure a malignant tumor of the intestinal tract. Pinworm infestation is common, but there is little evidence that this affects the incidence of appendicitis. Round worms, however, may occasionally form a matted mass in the large bowel of children, causing intestinal obstruction that requires surgical relief. These complications are relatively rare, and surgery in the tropics, contrary to popular impression, does not deal solely with problems of parasitic disease but is similar to surgical practice in temperate zones with only an occasional exotic problem peculiar to warm countries.

Peripheral Vascular Disease

Peripheral vascular disease in the tropics differs in several respects from similar conditions in America. The most prominent contrast is the scarcity of varicose veins. Despite the fact that many of these people are on their feet for long periods and have multiple pregnancies, varicosities are rare. The general lack of obesity among the people may be a factor in the absence of this condition.

Leg ulcers in temperate zones usually result from peripheral vascular insufficiency. In the tropics, on the other hand, chronic infection is much more frequently the cause of the ulceration. Ulcers due to mixed fungous and bacterial infection were well known to American medical officers in the Southwest Pacific during World War II. These persistent, ragged ulcerations, commonly referred to as jungle rot, usually responded quickly to simple cleanliness, rest and elevation of the extremity. Occasionally, diphtheria organisms were found in these ulcers and rarely caused remote signs of toxicity such as diphtheritic carditis.

The disabling leg ulcers resulting from yaws or frambesia are extremely common in many parts of the tropics. This nonvenereal treponema infection has many protean manifestations, one of the commonest of which is a persistent ulceration of the lower leg. Penicillin is so effective in the treatment of yaws that a therapeutic trial is usually given to patients with leg ulcers before more remote causes of ulceration are investigated. When such ulcers have persisted for prolonged periods, even the eradication of infection will not result in adequate spontaneous skin coverage and grafting is often necessary.

Another vascular problem that for some obscure reason is common in Thailand is thromboangiitis obliterans, or Buerger's disease. This vasospastic disease appearing in young and middle-aged men and characterized by clinical signs of arterial insufficiency may or may not be true Buerger's disease, for microscopical examination of the involved tissue seldom has been performed. Lumbar sympathectomy is of definite value in the treatment of this condition. It has been suggested that this peripheral vascular disease is caused by standing in the water of rice paddies for long hours at a time. This popular conception has not been investigated. There does not seem to be any relation to ergot ingestion.

Miscellaneous Conditions

Typhoid fever continues to be a common clinical problem in many tropical countries. Surgeons in these areas must frequently evaluate typhoid patients for evidence of bowel perforation. Although constipation and severe abdominal distress are often early symptoms of typhoid fever, perforation appears later in the course of the disease, on about the tenth to the twelfth day. The patient is usually extremely ill before perforation, which is associated with a high mortality, even with the aid of proper antibiotic coverage. If chloramphenicol therapy can be given early in the course of the disease perforation is usually avoided.

A major plastic surgical problem now peculiar to the tropics is the repair of the horribly crippling effects of noma or cancrum oris (gangrenous stomatitis). This condition, which usually appears in malnourished or otherwise debilitated infants, consists of a necrotizing mixed infection of the entire thickness of the mouth and cheek that destroys the soft tissue from the buccal mucosa completely through to the skin, baring teeth and bone. Fortunately, penicillin usually will halt the progress of this infection, but often not before irreparable damage has been done. Soon after the active invasive process stops, the remaining muscles and soft tissues of the jaws become so scarred that the mouth cannot be opened. The jaws are closed as though by bony ankylosis, and nasal-tube feeding or even a gastrostomy may be required. Osteomyelitis of the exposed mandible occasionally occurs and requires soft-tissue coverage for its control. Because of the

great loss of skin this entails the raising of a large skin flap — a hazardous procedure in these undernourished infants.

An unexpectedly large number of cases of Cooley's anemia have been recognized in Thailand. Ordinarily, splenectomy is not thought to be indicated, but a number of Thai surgeons and hematologists now believe that removal of the spleen is of definite benefit and may decrease the need for further transfusion.[13]

Conclusion

This paper does not pretend to be an exhaustive analysis of all surgical problems peculiar to the tropics. The problems presented may be not only of passing general interest but also of aid in the management of patients who have lived or traveled in these parts of the world.

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LEUKEMOID BLOOD REACTIONS*

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THE apparent coincidence of leukemia and various infections, principally tuberculosis, was noted by various observers, mostly in the German literature, as early as 1900.[1] However, the first careful consideration of leukemia-like blood pictures as nonmalignant entities was in 1926 by Krumbhaar,[2] who coined the term "leukemoid" to describe them. Since bone-marrow biopsy as a diagnostic aid was not in general use at that time, coincidental leukemia cannot positively be ruled out in some of his cases. Indeed, it was found that many of the cases reported, including some widely cited by other authors, may have been truly leukemic, since some autopsies definitely showed typical leukemic infiltration of parenchymatous organs or even arrest of maturation in bone marrow.[3-5]

A leukemoid blood reaction may be defined as a nonmalignant leukocytosis of such character as to present problems in differentiation from the true leukemia, because of either mature leukocytosis of extreme degree or the presence of immature forms in the peripheral blood. In any discussion of this phenomenon certain arbitrary criteria must be adopted to exclude the leukocytoses of common clinical experience. Those used in this paper, taken in part from Hill and Duncan,[6] are as follows: in leukemoid reactions of the myeloid type, a white-cell count of over 50,000 alone or combined with the presence of more than 2 per cent myeloblasts and myelocytes in the peripheral blood; in the lymphoid type, a lymphocyte count of more than 40 per cent in the presence of immature forms in the peripheral blood; and in the monocytic type, a monocyte count of more than 30 per cent with a white-cell count of more than 30,000.

In the cases presented in this paper, leukemia was ruled out by one of the following: bone-marrow examination; rapid recovery from the acute episode without recurrence of leukocytosis during at least a year's follow-up period; or autopsy.

Although earlier authors believed that leukemoid reactions could be differentiated from leukemia on the basis of peripheral blood examination, with particular reference to the development of thrombocytopenia, anemia and basophilia in true leukemia, it has since been shown that leukemoid reactions may present any or all of these conditions.[2, 6-11] Conversely, a normal hemogram may exist in the presence of leukemia, especially that of the "aleukemic" type; consequently, bone-marrow examination is now the only certain method of differential diagnosis of these conditions. Recent studies[12] have demonstrated that the blood histamine level is markedly elevated in chronic myelogenous leukemia, but normal in other leukemias and in leukemoid reactions. It may be that further investigations along biochemical lines will produce reliable diagnostic procedures that may replace surgical biopsy of lymph nodes or other organs in the conditions in which marrow is unavailable, such as osteosclerosis.[6]

It is almost impossible to determine the incidence of leukemoid reactions from examination of hospital files because many cases are listed under the primary

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diagnosis only, and not as "leukocytosis" or "leukemoid reactions." An investigation of all cases listed under these two diagnoses in the files of the Johns Hopkins Hospital during the past fifty years produced 4 cases meeting the criteria for leukemoid reactions listed above. A survey of the medical literature in English revealed only 49 well documented and proved cases, and all authors reviewing the condition have commented on its extreme rarity in clinical experience. However, with the present use of routine blood counts and the universal availability of bone-marrow biopsy as a diagnostic aid, an increased apparent incidence may be expected. Although overwhelming bacterial and tuberculous infections are less commonly seen with the many antibiotics now available, some leukemoid reactions also may be expected on the basis of the known myelotoxic effects of certain of the newer antibiotics. Several cases that followed the use of sulfonamides were reported during the period of maximum use of these agents.[6, 9]

Table 1. *Leukemoid Reactions Reported in the Literature.*

Case No.	Basic Disease	White-Cell Count	Differential Count: Myelo-blasts	Myelo-cytes	Juvenile forms & band forms	Neutro-phils	Lympho-cytes	Mono-cytes	Eosino-phils	Baso-phils	Proof*	Author
			%	%	%	%	%	%	%	%		
1	Tuberculosis, caseating	220,000	4	53	8	29	3	—	—	2	Autopsy	Custer & Crocker[33]
2	Tuberculosis, chronic glandular	6,100	11	64†	—	1	24	—	—	—	Autopsy	Gardner & Mettier[34]
3	Tuberculosis, miliary, & teratoma	82,000	1	2	—	47	6	43	—	—	Autopsy	Gibson[8]
4	Osteomyelitis & multiple abscesses	78,400	—	20	55	25	2	—	18	5	Autopsy	Hill & Duncan[6]
5	Empyema, coliform bacilli	104,000	1	18	—	75	3	3	—	—	Biopsy	Smith[35]
6	Gonorrhea, secondary syphilis & Vincent's angina	15,200	—	44	—	8	48	—	—	—	Recovery	Krambhaar[3]
7	Mixed malarial infection	4,000	—	32	14	27	21	6	—	—	Biopsy	Riley & Robins[31]
8	Varicella	81,200	2	—	—	9	87	1	2	—	Recovery	Goldman[29]
9	Pertussis & lobar pneumonia	52,900	1	1	40	9	43	6	—	—	Recovery	Hill & Duncan[6]
10	Scabies (treated with mercury ointment)	26,300	9	33	16	22	17	7	3	1	Recovery	Downey et al.[39]
11	Lobar pneumonia (treated with sulfapyridine)	33,000	—	27	25	33	11	1	1	—	Biopsy	Goldbloom et al.[9]
12	Hodgkin's disease	54,400	—	—	—	55	10	—	32	2	Autopsy	Hill & Duncan[6]
13	Metastatic bronchiogenic carcinoma (to bone marrow)	144,000	—	1	48	47	2	2	—	—	Autopsy	Hinshaw & Hoxie[40]
14	Nonmetastatic gastric carcinoma	110,000	—	2	—	94	4	—	—	—	Autopsy	Meyer & Rotter[38]
15	Infectious mononucleosis	20,200	—	9	—	25	55	9	—	—	Recovery	Landon[18]
16	Sarcoidosis	6,600	—	—	—	18	78	4	—	—	Autopsy	Posner[28]
17	Osteosclerosis	10,500	29	6	24	27	8	—	—	2	Autopsy	Hill & Duncan[6]

*Proof of nonleukemic etiology.
†"Prolymphocytes."

Much of the literature on leukemoid blood reactions deals with those seen in tuberculosis,[13-16] but they also occur in diseases of bacterial,[17, 18] spirochetal,[19] viral[20] and protozoal[21] origin. Moreover, leukemoid reactions may develop in the presence of nonmyelogenic cancer,[22-24] and certain anemias[7, 11] or after the local or systemic administration of potentially toxic substances, such as mercury and sulfonamides. Table 1 is a compilation of data from representative cases of various types from the literature, a few of which require further comment.

The first 3 cases demonstrate that tuberculosis may simulate myelogenous, lymphogenous or monocytic leukemia. Case 7, a mixed infection with *Plasmodium vivax* and *P. falciparum*, resembles "aleukemic" leukemia, with a low normal white-cell count and large numbers of immature cells. Case 10 was one of three members of a family in whom leukemoid blood reactions followed treatment of scabies with a mercurial ointment, the application of which to rabbits failed to reproduce a reaction. Case 11 is representative of many reported with the use of sulfonamides, the reaction occurring when the pneumonic process was improving. Cases 13 and 14 showed similar counts in the presence of carcinoma — in 1 case confined to the stomach and, in the other, actually invading the bone marrow. In Case 17 autopsy revealed almost complete obliteration of the normal bone marrow, with ectopic hemopoiesis in the lungs, liver, spleen, kidneys and lymph nodes; it was thought that many of the cells seen were even more immature than the blast stage.

Case Reports

The following 2 new cases of leukemoid blood reactions present interesting features:

Case 1. W. H. (U.S.N.H. 208617), a 19-year-old boy, was admitted to the hospital, on December 7, 1952, suffering from acute glomerulonephritis.* The diagnosis of acute glomerulonephritis was established on the basis of a history of antecedent respiratory infection, clinical findings of pulmonary and pretibial edema, profound anemia (hematocrit of 17 mm.) and a urinary sediment containing granular and red-cell casts, free red and white cells in large numbers and a protein of 400 mg. per 100 cc.

Shortly after admission to the hospital the patient vomited coffee-grounds material, and 1 liter of blood was given intravenously without improvement in the hematocrit. He was given oxygen, antibiotics and lanatoside C, and a negative water balance was maintained throughout the following day. The pulmonary edema decreased, but the urinary sediment contained increased numbers of cellular casts. After the intravenous administration of 3 additional liters of blood, the hematocrit rose to 31 mm., at which level it remained.

The course from the 7th through the 22d hospital day was characterized by progressive decrease in urinary output, a rise in the blood urea nitrogen to 321 mg. per 100 cc., vomiting, persistent proteinuria (about 500 mg. per 100 cc.), a correctible sodium deficiency and persistent hyperkalemia, the serum potas-

*A survey of the medical literature in English disclosed no report of a leukemoid reaction in this condition.

sium level rising to 9.5 milliequiv. per liter. An electrocardiogram on the 18th day gave evidence of potassium intoxication, which failed to improve on conservative therapy.

On the 22d hospital day, extracorporeal dialysis by means of an artificial kidney was instituted, reducing the blood urea nitrogen from 325 to 96 mg. per 100 cc. during the first 4 hours

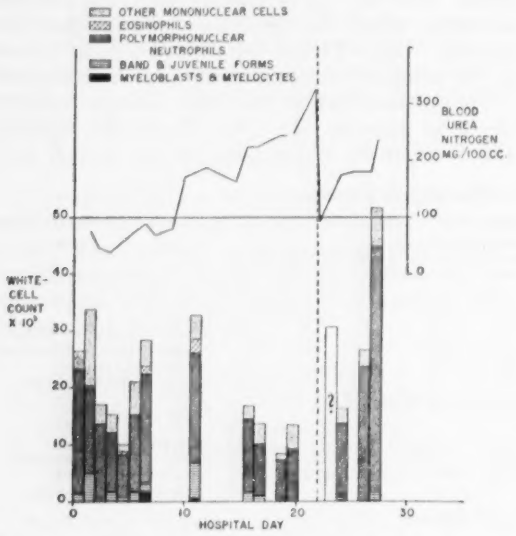

FIGURE 1. *Peripheral Leukocyte Counts and Blood Urea Nitrogen Levels in Case 1 (Patient with Acute Glomerulonephritis).*
The broken line represents the time of extracorporeal dialysis by means of an artificial kidney.

of the procedure. Because the concentration of serum sodium was reported at that time to have risen to 182 milliequiv. per liter, sodium was withheld from the dialysate bath when it was reconstituted. Hemolysis then occurred in the cellophane tubing of the apparatus, and the patient received an estimated 200 or 300 cc. of hemolyzed blood before the connections were clamped off.

Immediately after dialysis the patient's clinical condition improved markedly, and vomiting ceased. On the next day, however, gross facial and periorbital edema and hepatomegaly developed, and repeated convulsions occurred until he was heavily sedated. The hematocrit, which had fallen after the dialysis, reached a level of 19 mm., where it remained in spite of the administration of 1200 cc. of packed red cells.

On the 27th hospital day severe pulmonary edema and venous distention again developed, with marked respiratory distress. The serum potassium was reported as 8.2 milliequiv. per liter, and an electrocardiogram taken at noon showed marked "QRS" changes typical of hyperkalemia. The patient's condition deteriorated, and he died at 4:35 p.m. Autopsy revealed changes consistent with subacute glomerulonephritis.

This patient presented four distinct leukocytic episodes (Fig. 1). The first, immediately after admission, coincided with pulmonary edema and severe anemia. It is of interest that this episode involved a moderate lymphocytosis (the white-cell count on the second hospital day was 33,600, with 8 per cent band and 6 per cent juvenile forms, 46 per cent neutrophils and 40 per cent lymphocytes), whereas the other rises were composed almost entirely of cells of the myelocytic series. The second peak occurred during a period of relative remission of clinical symptoms, after intensive antibiotic therapy. Although it coincided with the beginning of the rise in blood urea nitrogen, the white-cell count soon dropped whereas nitrogen retention increased. This peak on the ninth hospital day is notable because of a moderate eosinophilia (count of 5 per cent) and the appearance of myeloblasts (5 per cent) in the peripheral blood, with increased juvenile and band forms (on the eleventh day the white-cell count was 32,500, with 1 per cent myelocytes, 9 per cent band and 9 per cent juvenile forms, 63 per cent neutrophils, 10 per cent lymphocytes, 1 per cent monocytes and 7 per cent eosinophils). The third peak immediately followed the injection of hemolyzed blood. Unfortunately, no differential count was made at this time. The final and most dramatic rise occurred on the day of death, when the white-cell count was 51,900, with 2 per cent band forms, 87 per cent neutrophils and 11 per cent myelocytes, and was associated with increasing

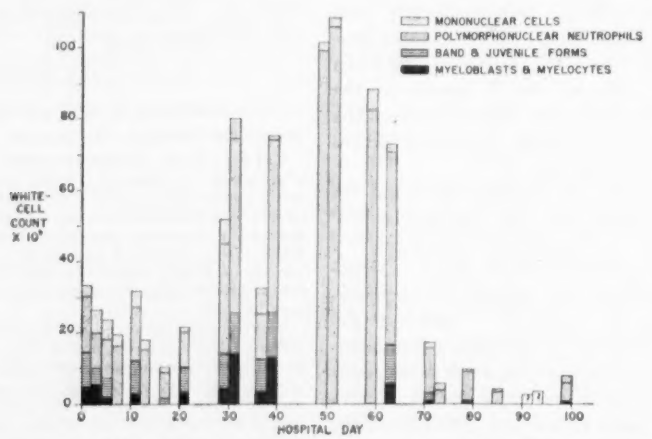

FIGURE 2. *Peripheral Leukocyte Counts in Case 2 (Patient with Miliary Tuberculosis).*

pulmonary edema, precipitous rise in blood urea nitrogen and marked hyperkalemia; however, both the blood urea nitrogen and the potassium had reached higher levels during periods of relatively low white-cell count.

CASE 2. J. H. (U.S.N.H. 125514), a 20-year-old Negro, was seen at the United States Naval Hospital, St. Albans, New York, to which he had been transferred from another hospital on December 27, 1951.

He was first admitted elsewhere on September 18, with a 2-day history of swelling and cramping pain in the abdomen after a fall. The family and social histories were noncontributory; the past history was irrelevant except for "spinal meningitis" without sequelae at the age of 15. Physical examination was within normal limits except for a temperature of 101.4°F. and a large, very tender mass, assumed to be the spleen, filling the left upper quadrant of the abdomen. The patient was apathetic and appeared chronically ill. Blood studies showed a moderate anemia (hemoglobin of 9.5 gm. per 100 cc.) and a mild leukemoid blood picture (white-cell count of 32,000, with 14 per cent myelocytes, 13 per cent juvenile and 16 per cent stab forms, 45 per cent neutrophils, 10 per cent lymphocytes and 2 per cent monocytes). Other laboratory procedures, including urinalysis, heterophil-antibody agglutination, sickling preparation, van den Bergh test and malarial smears, were negative. X-ray examination of the chest demonstrated scattered granular densities throughout both lung fields, with an area of coalescence in the right upper-lung field.

The patient was given penicillin on the day of admission, followed by a 3-day course of chloroquine, without effect on a persistent temperature of 101-104°F. Although gastric washings for tubercle bacilli had been reported as negative, a course of streptomycin and PAS was begun on the 10th hospital day "because of his wasted appearance, fever and chest findings" and a positive reaction to 2d-strength PPD (purified protein derivative), which became negative. The temperature fell to normal levels, but it was stated that "the patient's response to chemotherapy was not remarkable," and both drugs were discontinued on the 28th hospital day; the temperature subsequently rose to a daily average of 101°F. The white-cell counts are shown in Figure 2. Because of the persistent leukocytosis after admission, a bone-marrow biopsy was done on the 24th hospital day and the marrow was reported as "typical of leukemoid blood reaction." Shortly thereafter, a marked upswing in the peripheral white-cell count (to a level of 80,000) occurred; there was an initial rise in the immature cells (16 per cent myelocytes, 7 per cent juvenile and 8 per cent stab forms, 63 per cent neutrophils and 6 per cent lymphocytes), but the peak of the reaction, on the 52d hospital day, consisted entirely of mature neutrophils (98 per cent) and eosinophils (2 per cent), with a white-cell count of 108,000.

Despite the report of the bone-marrow biopsy, chronic myelogenous leukemia was considered the most likely diagnosis. Urethane, 2 gm. per day, was administered from the 42d through the 73d day, when it was stopped because of the marked depression of the peripheral white-cell count, which reached a low of 2600 on the 92d hospital day (differential not properly recorded). A bone-marrow biopsy on the 78th day was reported as "not remarkable," but a 3d biopsy shortly after transfer to St. Albans Hospital, on the 108th day, showed marked pancytopenia. Culture for tubercle bacilli was negative.

At this time, early in January, 1952, x-ray examination of the chest showed diffusely disseminated nodules, mostly of miliary size. Biopsy of a nodule in the epididymis revealed *Mycobacterium tuberculosis*. The diagnosis of hematogenous tuberculosis was confirmed by culture of tubercle bacilli from gastric washings and spinal fluid. It was noted that PPD skin tests were negative in 1st and 2d strengths.

Clinical signs of meningitis, which cleared only partially on streptomycin and para-amino salicylic acid (PAS) therapy, developed. Later x-ray films showed cavitation in the lungs, which progressed in spite of artificial pneumothorax. The patient became stuporous with the return of meningeal signs on the 182d day and died quietly on the 189th. Permission for autopsy was refused. The white-cell count during his admission to St. Albans Hospital varied between 4000 and 12,000, with normal differential counts, until the day before death, when it suddenly rose to 22,800, with 1 per cent band forms, 94 per cent neutrophils and 5 per cent lymphocytes.

DISCUSSION

The search for an explanation of these reactions has interested several investigators. Hill and Duncan[6] presented a comprehensive discussion of the problem and suggested three basic mechanisms: direct stimulation of the bone marrow by mechanical invasion, actual infection of the marrow or intramedullary antigen-antibody reactions, as in heterologous transfusions; "marrow response to an overwhelming demand" in the presence of hemolysis or anemia; and ectopic hemopoiesis secondary to prolonged demand on, or obliteration of, the normal bone marrow. They believed that toxic damage to the endothelium of the marrow may allow immature cells to be washed prematurely into the peripheral blood. Similarly, Heck and Hall[11] suggested that immature cells in abnormal locations may be intravascular and therefore easily washed loose into the circulating blood. None of these mechanisms satisfactorily explain the severe reactions seen in the presence of localized primary cancer of parenchymal organs. Arneth[32] considered a selective chemotactic effect of toxic substances on a single cell type, and Sonnenfeld[22] compared tumor products to a parenteral injection of protein in producing leukocytosis.

Feldman and Stasney[1] inoculated rabbits with tubercle bacilli of human and bovine strains and later produced white-cell counts as high as 124,000 by the injection of tuberculin (normal level, 11,000). They mention 3 cases of leukocytosis in human beings that followed tuberculin administration reported in the German literature, and suggest that endogenous tuberculin-like products may produce such reactions in sensitized persons.

Recently, work has been done to elucidate the usual mechanism of leukocyte regulation in the body. Weisberger et al.[33] obtained lymphocytes from the thoracic ducts of laboratory animals and injected them into the same animals intravenously in massive quantity. They noted that the total white-cell count in other peripheral veins was depressed rather than elevated after this procedure, and at autopsy the alveolar membranes of the lungs were filled with lymphocytes. Lanman et al.[34] injected dye-containing leukemic blood into patients with inoperable cancer. Blood was obtained by direct puncture and catheterization from various points in the cardiovascular circuits, and the measured white-cell count was compared with that predicted by dilution of the dye. It was found that the count was markedly reduced between the right ventricle and the systemic arteries, and that it returned to preinjection levels or below within a few minutes.

These studies strongly suggest that the lungs are a normal site of removal of leukocytes from the circulation. Since the circulating leukocyte count must represent a balance between production on the one hand and destruction or temporary re-

moval from the circulation on the other, failure of the normal mechanism of destruction or removal would presumably result in a rise in the count. The hypothesis is advanced that some leukemoid reactions result from embarrassment of the normal leukocytophagic function of the lungs, as by invasion, massive infection or pulmonary edema.

A review of evidence of the mechanism responsible for the leukemoid reactions in the 2 cases presented above indicates that the multiple peaks in Case 1 preclude any single explanation. The first rise (Fig. 1) occurred during a period of severe anemia and pulmonary edema. Either bone-marrow response to overwhelming demand or embarrassment of the lungs might be suggested as a cause. The second peak, as noted, followed heavy administration of antibiotics and occurred during clinical remission of the previous symptoms. Of the hypotheses presented, only that of a toxic reaction seems tenable for this episode. The third peak followed dialysis and hemolysis, but preceded by a day the sharp fall in hematocrit, so that a reaction to the presence of free hemoglobin must be assumed. The fourth, and agonal, episode coincided with anemia, pulmonary edema and a rise in the blood urea nitrogen. There was no evidence at autopsy of embarrassment of the bone marrow or of extramedullary hemopoiesis.

The case of the patient with miliary tuberculosis may present some evidence for the "lung damage" hypothesis to the extent that other possible mechanisms may be excluded in the presence of known overwhelming pulmonary infection. Repeated bone-marrow biopsies and one culture failed to demonstrate any infection. There was no marked anemia, and although extramedullary hemopoiesis cannot be ruled out absolutely, there was no evidence of its presence. An antigen-antibody reaction, then, seems the most likely cause, except that the patient's failure to respond to first-strength PPD at the time of the reaction, and to second-strength later, suggests that his capacity for allergic response was practically exhausted. Unfortunately, the natural history of the reaction was interrupted by urethane; persistence or lysis of the leukocytosis would have been very informative in the presence of progressing lung lesions and increasing anergy.

In view of the rarity of leukemoid reactions, and the frequent occurrence of conditions that seem adequate to produce them by one or more of the mechanisms suggested, it appears that certain persons, such as the patient in Case 1, have inherent predispositions to these reactions, possibly on a familial basis.

Summary

Criteria for the diagnosis of leukemoid reactions are discussed.

Selected cases from the literature are briefly reviewed.

Two cases are reported, the first being an example of multiple leukocytoses of various differential composition in a patient with acute glomerulonephritis and the second a myelocytic response, altered by urethane therapy, in a patient with miliary tuberculosis.

Previously advanced theories of etiologic mechanism of leukemoid reactions are discussed.

In view of recent work establishing a leukocytoregulatory function of the lungs, the hypothesis is advanced that certain leukemoid reactions may be caused by damage to the lungs, and evidence in support of this hypothesis is presented.

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PATHOLOGICAL MANIFESTATIONS IN AN INFANT AFTER MATERNAL RUBELLA IN THE SIXTEENTH WEEK OF GESTATION*

Report of a Case

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BOSTON

Gregg's[1] observation that rubella in the mother during early pregnancy frequently leads to congenital cataract of the unborn child has been confirmed by numerous investigators.[2-4] The effects of the maternal infection on the conceptus vary within a broad range of possibilities: the fetus may escape injury, die or have various combinations of defects as late manifestations — arrested or distorted development of the eyes with anomalies of the teeth, middle ear and heart.[2] Rubella is most likely to cause cataract (usually nuclear) when the infection occurs at the fourth to the sixth week of gestation.[2, 5] The observation is consistent with knowledge that this is the period of most active proliferation of the primary fibers that fill the optic lens during the second month of fetal life. However, differentiation continues over a considerable span of early pregnancy,[6] and herein lies much of the interest of the case reported below. After maternal rubella in the fourth month of pregnancy, pathological changes were observed in the peripheral portion of the lens of the infant, born at term but dying in the neonatal period. Additional points of interest in this case were associated manifestations of acute panophthalmitis, a condition hitherto not described in conjunction with postrubella congenital cataract, and renal changes, mainly hyalinization of glomeruli.

Common features in 3 cases of postrubella malformations studied at autopsy by Swan[7] included prematurity (Cases 1 and 2), congenital heart disease (Cases 1, 2 and 3) and cataractous changes of the lens (Cases 2 and 3). All the infants had been born of mothers who had contracted rubella during the second month of gestation, and none of the 3 had survived more than ten weeks after birth. Swan confirmed Gregg's clinical impression that the cataractous change of the lens differed substantially from that usually seen in later life. The nuclear portion showed "necrosis en masse," and the lens fibers of the equatorial region were disoriented and distorted. In all 3 cases examination of the kidneys demonstrated partial or complete replacement of the tufts of the glomeruli by hyalinized fibrous tissue, with adhesions between the parietal and visceral layers of the Bowman capsule. Swan concluded that the pathological changes of the eye and of the heart are only the more obvious manifestations of a widespread attack by the virus of rubella upon the tissues of the embryo. Swan[7] also had the rare opportunity to study the ocular changes of an embryo obtained shortly after the mother contracted rubella late in the second month of pregnancy. The left eye was normal, whereas the right already disclosed considerable disorganization, including microphthalmos, cataract formation, diminution of the vascular supply of the lens and failure of closure of the fetal fissure.

Terry[8] studied the eye of a four-month-old baby who had suffered the effects of maternal rubella at the third month of intrauterine life. The fetal nucleus of the lens almost touched the anterior pole of the lens, a finding that he interpreted as indicating that the lens fibers were prevented from growing forward and inserting themselves in front of the nucleus. The ciliary body showed lack of development, and the rods and cones of the retina were poorly differentiated. There were small retinal ganglion cells, a poorly formed meshwork in the angle of the iris and failure of the anterior surface of the iris to undergo atrophy.

Cordes and Barber[9] studied the eyes of an embryo recovered after therapeutic abortion performed at eight weeks because of rubella in the mother during the fifth week of gestation. Although the posterior segment of the eye was normal, the lens showed definite retardation of growth and differentiation. The interpretation was made that absence of the protection of the lids and of the Descemet and Bowman membranes during the first three months of development is the factor that permits "the toxic agent in the amniotic fluid to act fairly directly on the lens during this time." After rubella in the mother, cataractous change was already present in the 25-mm.-long embryo obtained by Helweg-Larsen and Nielsen.[10] The lens was underdeveloped, with fibers that disclosed fine vacuolization and did not fill its cavity. Comparable changes were seen by Cordes[11] in an eleven-week-old embryo obtained after therapeutic abortion from a mother who had had rubella during the latter part of the second month of pregnancy. The capsule of the lens was present and intact, but most of the primary and secondary fibers showed degeneration and lique-

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faction, with formation of globules and homogeneous masses of dark-staining material.

Observations that have been made to date have failed to contribute any explanation of the development of the malformations that follow the maternal infection. Most investigators have taken for granted that the virus of rubella enters the embryo through the placenta, but the matter remains speculative. It seems just as possible that if the placental capillaries partake in this widespread erythematous disturbance manifested by the skin, the impact of infection on the fetus is indirect and of a metabolic nature. Whatever its mechanism, the teratogenic effect on the embryo is widespread and involves many tissues, and it is reasonable to assume that this action is mediated through the vascular system.

Case Report

Maternal History

A 35-year-old para IV had been delivered of her 3d child by cesarean section, because of placenta praevia. At the 16th week of her last pregnancy she contracted rubella. Except for this mild infection, pregnancy progressed without difficulty until

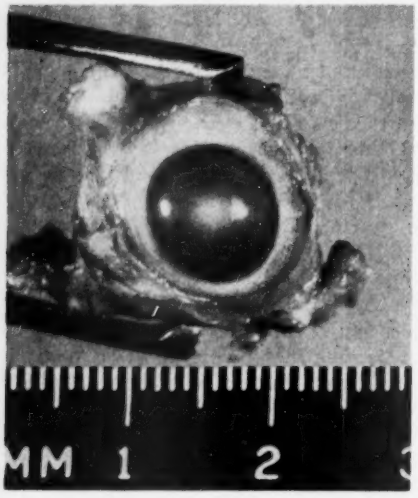

Figure 1. *Photograph of the Right Eye, Showing Opacity of the Lens.*

3 weeks before term, when epigastric pains, accompanied by tenseness of the uterus and progressive elevation of the systolic blood pressure, developed. Examinations of the urine were negative. She was delivered by cesarean section and made a good operative recovery.

History of the Infant

At birth the baby weighed 5 lb., 3 oz., manifested shallow respiration and progressively poorer vitality and died at the end of the 1st day of life.

Post-Mortem Findings

External examination showed a relatively well developed premature infant with bilateral cataract (Fig. 1). Otherwise, no gross abnormalities were observed in the head, chest and abdomen, except for diffuse atelectasis of the lungs.

Microscopical Study

Description is limited to findings in the kidneys and the right eye; the left eye was not removed. No lesions of specific interest were detected in the other viscera, including the brain, myocardium, lungs, thymus, liver, spleen, stomach, intestines, pancreas, thyroid and adrenal glands and testicles.

Right eye. The size, shape and general configuration of the eyeball were not unusual. Anterior and posterior chambers were

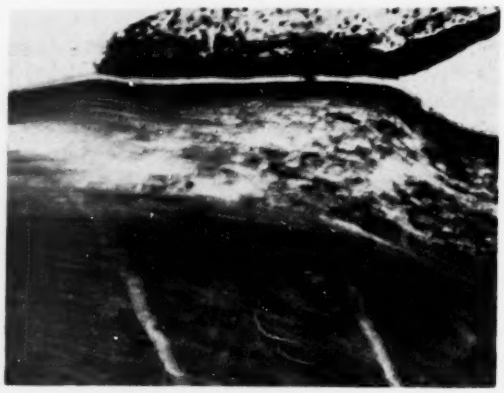

Figure 2. *Disintegration and Vacuolization of the Cortical Lens Fibers (X400).*

Note the posterior synechia between the iris and the anterolateral portion of the lens capsule.

well developed, and both the space of Fontana and the canal of Schlemn were clearly made out. The ciliary body was, however, hypoplastic, and the iris showed a posterior synechia between the central margin and the adjacent anterolateral portion of the lens capsule (Fig. 2); in one area, where the synechia had been ruptured, the pigment layer of the iris adhered to the capsule

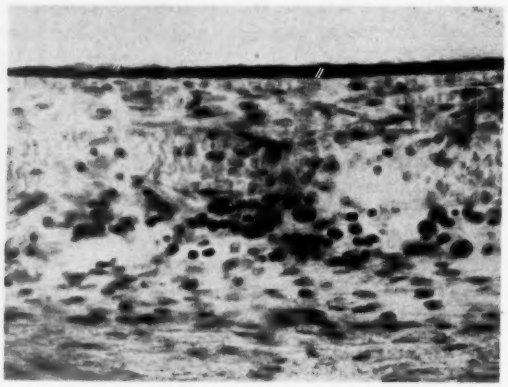

Figure 3. *Vascular Engorgement and Massive Infiltration of Round Cells and Eosinophilic Granulocytes in the Choroid (X400).*

of the lens. The cataractous change at the periphery of the lens was characterized by disintegration of lens fibers, with replacement by vacuoles of various dimensions (Fig. 2). The anterior portion of the capsule demonstrated epithelial proliferation, interpreted by us as an abortive attempt at new fiber formation.

Vascular changes and scattered foci of inflammatory cells, chiefly at perivascular localizations, were noticeable in several ocular structures. These inflammatory foci consisted of round cells, plasma cells and histiocytes interspersed with numerous eosinophilic granulocytes. Foci with these characteristics were

present in the conjunctival fornices and in the subepithelial connective tissue of the bulbar conjunctiva, sclera and choroid (Fig. 3 and 4), mainly in the posterior portion of the eye.

The blood vessels of the eye were engorged throughout. This was most apparent in the uveal tract and in the retina, which was detached in a segment extending from the optic nerve to the ora serrata. Two nodular elevations, interpreted as *Drüsen*, were present in the pigmented layer. They were characterized by epithelial proliferation and localized thickening of the subjacent Bruch membrane. Serous material and extravasated red cells were observed in the layer of the inner nerve fibers, which showed diffuse vascular engorgement with thrombosis of thin-walled blood channels that appeared to be of recent origin.

Kidneys. Occasional glomeruli in both organs showed fibrous thickening of the parietal layer of the Bowman capsule, sometimes with adhesions between the parietal and visceral layers of the capsule and relative obliteration of the glomerular space. The fibrous stroma between tufts was more abundant than normal; in places there was proliferation of endothelial cells in the capillary loops, resulting in narrowing of lumens, and some glomeruli displayed partial or complete replacement by hyalinized fibrous tissue (Fig. 5). The proximal convoluted tubules were dilated and often revealed swelling and vacuolization of the renal epithelium, with occasional desquamation of cells. Focal hemorrhages were present in the region of the papillae, which displayed pronounced vascular engorgement.

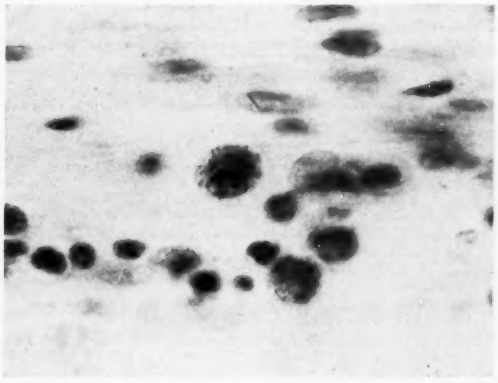

FIGURE 4. *Section from the Same Field as Figure 3, at Higher Magnification (X1200), Showing Polymorphonuclear Leukocytes Containing Large Cytoplasmic Eosinophilic Granules.*

DISCUSSION

Experimentally it has been shown that a teratogenic agent may result in two basically different kinds of anomaly. One consists of ablation, stunting or distortion of structure of a type that is not observed after differentiation of the tissue is complete; the other includes regressive and proliferative changes of types encountered in postnatal life as a response to injurious processes.[12] Hypoplasia of the ciliary body of the eye, observed in the case reported above, exemplifies a change that belongs in the first category; the cataractous change within the lens, the detachment of the retina, the posterior synechia, the foci of inflammatory cell infiltration and the vascular phenomena, including congestion, thrombosis, and hemorrhage, are examples of responses that can occur in the prenatal, juvenile or adult stages of life.

The acute vascular and inflammatory changes can hardly be interpreted as manifestations of rubella five months after the event. A more likely explanation is that they represent — in great part, at least — agonal sequences secondary to hypoxia — in turn consequent to pulmonary atelectasis. Yet this condition does not explain some unusual features of the cellular reaction, mainly characterized by an infiltration of polymorphonuclear leukocytes of the eosinophilic type. Although the relation of allergy to eosinophilia is not clear, eosinophilic leukocytes in increased number are associated with the hypersensitive state. Since lens protein is known to have antigenic properties[13-16] it is possible that allergy to lens proteins, released during the embryonic period, played a role in the morbid process discovered at autopsy.

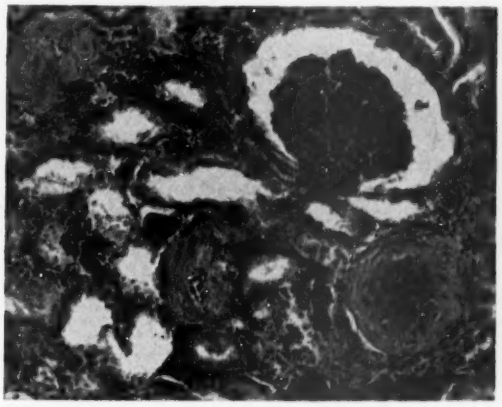

FIGURE 5. *Hyalinized Renal Glomeruli (X100).*

Renal changes, comparable to those noticed in the case presented above, mainly fibrosis and hyaline degeneration of the tufts and capsules of the glomeruli, were present in the three cases of Swan[7] and were interpreted as a manifestation of the widespread attack of the virus of rubella upon the tissues of the embryo. That such changes are probably nonspecific, certainly not always specifically due to rubella, is indicated by the studies of Herxheimer,[17] who found that glomerular fibrosis and hyalinization occurred in the kidneys of 38 of 43 infants dying shortly after birth or in the early months of life. Glomerular lesions of the kind under consideration were also found in 45 of 80 newborn infants examined after death by Schwarz[18] and by Friedman, Grayzel and Lederer[19] in 30 of 100 infants consecutively studied at autopsy. In 5 of 17 stillborn infants with hyaline changes of the glomerulus (nephrosclerosis) the mothers were recorded as having had syphilis, active, latent or cured. Otherwise, the incidence of maternal manifestations was not remarkable. Some of the mothers

had had colds during pregnancy, but whether this played any significant role could not be ascertained. The renal findings in the cases of Swan and those in the case reported above show that congenital glomerulosclerosis can also be found in infants in association with other postrubella manifestations, but this does not necessarily indicate that the virus of rubella was the cause of the glomerular changes.

Summary

The case of a male infant delivered by cesarean section, three weeks before term, of a mother who had contracted rubella during the sixteenth week of pregnancy is reported. There were cataractous changes in the periphery of the lens of the right eye and associated manifestations of acute panophthalmitis, including vascular thrombosis and striking infiltration of polymorphonuclear leukocytes of the eosinophilic type.

It is suggested that lens protein released during the embryonic period played the role of a sensitizing factor. Coexisting renal changes, mainly characterized by fibrosis and hyaline degeneration of the tufts and capsules of the glomeruli, may be interpreted as nonspecific, late manifestations of the widespread attack of the virus of rubella upon the tissues of the embryo.

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THE INCIDENCE OF PORTAL CIRRHOSIS AND FATTY METAMORPHOSIS IN PATIENTS DYING WITH DIABETES MELLITUS*

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BOSTON

THERE is a discrepancy in the literature regarding the incidence of portal cirrhosis in patients suffering from diabetes mellitus. It was therefore considered advantageous to study the livers from diabetic patients autopsied at the Peter Bent Brigham Hospital.

Schleusner[1] reviewed 355 autopsy protocols of diabetic patients in Hamburg dying between 1930 and 1936. He found 45 cases (12.7 per cent) with macroscopic evidence of cirrhosis. He noted that only a third were advanced and diagnosed clinically. The diabetes antedated the cirrhosis in 20 available clinical histories. At the other extreme, Joslin et al.[2] reported cirrhosis to be an uncommon complication, an incidence of 0.44 per cent being described among 20,094 diabetic patients admitted to the Deaconess Hospital from 1941 to 1950. Wilder[3] found evidence of cirrhosis or hepatitis in 0.7 per cent of 2584 diabetic patients at the Mayo Clinic between 1935 and 1937. Recently, Leevy, Ryan and Fineberg[4] performed hepatic studies on 380 diabetic patients, 38.9 per cent of whom gave evidence of hepatic dysfunction as evidenced by abnormalities in at least two liver-function tests. They considered "fatty livers" to be present when more than 10 per cent of the parenchymal cells were fat laden. Liver biopsies were performed on 8 diabetic patients with normal liver function. Five were reported as normal, and 3 showed fatty metamorphosis. Liver biopsies were also performed on 22 diabetic patients with varying degrees of hepatic dysfunction, being reported normal in 9, and as showing fatty metamorphosis in 5 and portal cirrhosis in 8. The authors further noted that with major abnormalities in liver function, a close correlation existed. There was a disassociation of structure and function with slight hepatic dysfunction.

Reinberg and Lipson[5] concluded that no significant difference existed between the incidence of

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cirrhosis in diabetic and nondiabetic persons. Zimmermann et al.[6] studied liver biopsies from 28 patients with uncomplicated diabetes mellitus and found 14 with fatty metamorphosis and 3 with cirrhosis.

It is generally agreed that fatty metamorphosis is relatively common in diabetes mellitus. Likewise, it is generally well recognized that fatty infiltration precedes portal cirrhosis.[7] It thus seems likely that portal cirrhosis should be more common in diabetic patients.

Material and Methods

The livers of diabetic patients who came to autopsy at the Peter Bent Brigham Hospital from 1928 to 1950 comprise the material for this study, 193 autopsies having been performed on such patients during this period. Sixteen of these cases were complicated by metastatic tumor to the liver or hemachromatosis, or no microscopical sections or material was available for study. This left 177 cases suitable for study. One control series included consecutive autopsies in 1935-1936. This series deleted cases for reasons mentioned above and endeavored as far as possible to select cases of comparable age and sex. There were 177 cases in this series. A second less rigid set of controls consisted of all cirrhotic patients on whom autopsies were performed between 1938 and 1950. Microscopical sections of all the livers in the diabetic patients and first control series were examined. The same criteria were applied to both series in the evaluation of structural abnormalities of the liver. In the second control series, only the autopsy protocols were examined.

Table 1. *Incidence of Portal Cirrhosis and Fatty Metamorphosis in Patients Dying with Diabetes Mellitus.*

Clinical or Autopsy Finding	No. of Cases	
Grade 1 cirrhosis	13	(7.3%)
Grade 2 cirrhosis	10	(5.7%)
Grade 3 cirrhosis	5	(2.8%)
Grade 4 cirrhosis	1	(0.5%)
Total	29	(16.3%)
Grade 1 fat	48	(27.1%)
Grade 2 fat	32	(18.0%)
Grade 3 fat	18	(10.1%)
Grade 4 fat	3	(1.6%)
Total	101	(57.0%)
Alcoholic history	6	(3.3%)
No alcoholic history	23	(13.0%)

Sections of the livers were fixed in 10 per cent formalin, Zenker's solution or Bouin's fluid. The sections were stained routinely with hematoxylin and eosin or phloxine and methylene blue. In many cases sections stained with Mallory's aniline blue, phosphotungstic acid-hematoxylin, Masson's trichrome, Sudan 4 for fat or iron reaction with potassium ferrocyanamide, or both, were utilized. The degree of fatty metamorphosis and cirrhosis was arbitrarily graded from 1 to 4.

The criteria for the diagnosis of portal cirrhosis were those of Himsworth.[8] The connective-tissue proliferation had to be diffuse to warrant a diagnosis of cirrhosis. Fatty cysts as described by Hartroft[9] were present in the majority of cases; "alcohol hyaline" was frequently present. The absence or minimal presence of bile stasis was also considered necessary to establish the diagnosis. Subcapsular fibrosis, occasionally simulating a focal picture of cirrhosis, was the most confusing condition to separate from portal cirrhosis. This finding might be particularly difficult to assess in a surgical biopsy of the liver. Fatty metamorphosis was considered to be present when more than 10 per cent of the liver cells contained fat vacuoles.

The clinical records of all the diabetic patients with cirrhosis and the cirrhotic patients in the first control series were examined. An attempt was made to correlate age, sex, duration of diabetes, age at onset of diabetes, severity, control, history of alcoholism and history of infectious hepatitis or hepatoxins with cirrhosis. The autopsy protocols were examined for size of liver, macroscopic description of the liver and description of the gall bladder and biliary tree.

Table 2. *Incidence of Portal Cirrhosis and Fatty Metamorphosis in 177 Patients Dying from Conditions Other than Diabetes Mellitus.*

Clinical or Autopsy Finding	No. of Cases	
Grade 1 cirrhosis	5	(2.8%)
Grade 2 cirrhosis	6	(3.3%)
Grade 3 cirrhosis	3	(1.6%)
Grade 4 cirrhosis	1	(0.5%)
Total	15	(8.4%)
Grade 1 fat	22	(12.4%)
Grade 2 fat	27	(15.2%)
Grade 3 fat	7	(3.9%)
Grade 4 fat	8	(4.5%)
Total	64	(36.1%)
Alcoholic history	8	(4.5%)
No alcoholic history	7	(3.9%)

Results

Table 1 presents the cases of portal cirrhosis and fatty metamorphosis in the diabetic series according to grade. Grade 1 portal cirrhosis represents a slight increase in periportal connective tissue, with trapping of groups of liver cells and extension into the periphery of liver lobules. The lobular distortion is minimal in this grading. Grade 4 signifies a severe distortion of lobular architecture, with central veins frequently at the periphery of liver lobules; there is a marked increase in the connective-tissue content of the liver. Grades 2 and 3 represent intermediate degrees.

Grade 1 fatty metamorphosis denotes fat-containing vacuoles in the cytoplasms of approximately 10 per cent of liver cells. Grade 4 fatty metamor-

phosis indicates fatty vacuolation of practically every liver cell. Grades 2 and 3 are intermediate in fat content.

Table 2 presents a similar grading of the first control series.

The second control series consisted of 4401 postmortem examinations performed at the Peter Bent Brigham Hospital between 1928 and 1950. There were 172 cases diagnosed as portal cirrhosis in this interval: an incidence of 3.9 per cent. The discrepancy between the first and second control series can probably be accounted for by two factors. In the first place the diagnosis was listed in the anatomic diagnoses only when it was contributing to the cause of death or was the major pathological finding. Secondly, the criteria in a constantly changing population of prosectors vary from year to year.

The ages of the patients with diabetes and cirrhosis varied from thirteen to seventy-nine years with a mean of fifty-nine-and-seven-tenths years. There were 15 female and 14 male patients. In 6 cases the onset of the diabetes could not be determined. These patients entered the hospital in diabetic coma or severe acidosis, and this represented the first knowledge of the patient or the family of diabetes. The duration of the disease in the remaining patients varied from more than one year to twenty years. The diabetes was classified as severe in 12 cases, moderate in 10 and mild in 5; in 2 it was not specified. Hepatomegaly was noted in 22 patients. Liver-function tests were performed on only 8 patients and were abnormal in all.

The livers varied in weight from 960 to 4600 gm. Eleven livers weighed more than 2 kg. Two patients displayed calculi in the gall bladder, and 1 had calculi in the gall bladder and the common bile duct. The prosector in the last case found no evidence of complete obstruction or dilatation proximal to the calculus. There was no clinical indication of hepatitis or exposure to hepatoxins in any of the patients. Six (3.3 per cent) diabetic patients gave a history of alcoholism, whereas 8 (4.5 per cent) nondiabetic patients admitted to excessive use of alcohol.

Discussion

It appears that the incidence of portal cirrhosis was statistically greater in the diabetic than in the nondiabetic patients. (Any percentage greater than 3.84 is statistically significant.) Likewise, there was an appreciably greater incidence of fatty metamorphosis in the diabetic than in the nondiabetic patients.

It is generally agreed that an accurate diagnosis of alcoholism is difficult to obtain. Yet more nondiabetic than diabetic patients admitted excessive use of alcohol. Patients with diabetes are invariably told to refrain from excessive intake of alcohol, and it seems logical that there would be less alcoholism among them.

The role of alcohol in the pathogenesis of fatty metamorphosis and portal cirrhosis is still a moot question. Most observers[7, 8] recognize that alcohol is probably a "conditioner" through impairment of appetite, producing a nutritional deficiency, especially of essential amino acids. It is generally acknowledged that fatty metamorphosis and portal cirrhosis are more frequent in chronic alcoholism.

It was difficult to appraise the effect of severity, duration and control of diabetes on cirrhosis. The clinical records were frequently incomplete in this respect. There was a suggestion, however, of a higher incidence of cirrhosis in the severer degrees of diabetes and the cases that were poorly controlled.

Portal cirrhosis was a major contributory cause or the major cause of death in 11 of the 29 diabetic patients with cirrhosis. Eight of these patients were considered nonalcoholic and 3 alcoholic. These findings suggest that diabetes accounted for a major part in at least 8 (excluding the 3 alcoholic patients) of the 177 deaths among diabetic patients in this series, or an incidence of 4.5 per cent. This appears to be a significant figure.

The diabetes mellitus preceded the cirrhosis as far as could be determined in most cases. It was impossible to be certain of this point in the 6 cases that were first diagnosed as diabetes on the final admission to the hospital. In 3 of these cases, diabetes was severe and was a major cause of death.

The grade of fatty metamorphosis closely paralleled the degree of cirrhosis in 24 cases. In 3, there was considerably more fat than cirrhosis. In 2 cases the fibrosis far exceeded the fatty metamorphosis. It appears that the fatty metamorphosis is reversible whereas the fibrotic process, although moderately inactive in 4 cases, was not reversible.

Summary

The livers of patients dying with diabetes mellitus from 1928 to 1950 were examined for evidence of portal cirrhosis. A total of 177 patients comprised this study and were compared with a similar number of patients serving as controls.

The incidence of portal cirrhosis in the diabetic patients was 16.3 per cent, whereas only 8.4 per cent of the control series were found to have cirrhosis. It was believed that this represented a statistically valid difference. Fatty livers were observed in 57 per cent of the diabetic as compared with 36.1 per cent of the nondiabetic patients. Cirrhosis played a major part in 4.5 per cent of the deaths from diabetes, excluding the alcoholic patients, in this series.

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MEDICAL PROGRESS

PRESENT-DAY CONCEPTS OF SHOCK*

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THIS review of recent progress in the understanding of traumatic shock covers the period of accelerated investigation stimulated by World War II.‡ This period is notable for the many precise observations of injured men. Amplifying these observations are a host of experimental studies, some producing the kinds of injury seen clinically, and others dealing with isolated components of the clinical syndrome. This report is given largely in terms of clinical observations of shock due to injury and blood loss, sepsis and myocardial infarction. Shock primarily due to loss of sodium and water is considered better dealt with in a more general discussion of fluid and electrolyte disturbances. A variety of current views regarding the first two topics are discussed fully in recent symposia.[4-6] Extensive bibliographies are given by Davis[7] and Wiggers.[8]

SHOCK DUE TO INJURY AND BLOOD LOSS

Each burn, bullet wound, laceration or other severe injury produces its own complex of local damage and ensuing complications and, in addition, a nonspecific metabolic and endocrine response.[9] When the injury is sufficiently severe, as in about 2.5 per cent of battle casualties at the Anzio beachhead,[10] these effects may be overshadowed by a rapidly progressive failure of the circulation known as wound shock.[11]

Pathogenesis

Observations on casualties during World War I called attention to a reduced volume of circulating plasma. Because red-cell counts were often found to be high, a selective loss of plasma was considered to be a fundamental feature of shock[12] and was attributed to a generalized increase in capillary permeability, produced by capillary anoxia and by toxic substances released from injured tissues.[12, 13] However, experimental studies before World War II demonstrated that fluid loss into the area of injury is sufficient in itself to account for the development of shock.[14, 15]

The clinical observations during World War II uniformly demonstrated a correlation between the severity of shock and the degree of reduction in circulating blood volume.[16-27] Shock of moderate or severe degree developed when the blood volume was reduced by about 35 to 40 per cent of its normal value. In extreme cases, the loss was as great as 75 per cent of the original blood volume. The blood was lost from and into the area of injury. When whole blood was lost predominantly, the hematocrit value remained unchanged until reduced by dilution as plasma volume was recouped from interstitial fluid. The hematocrit rose only when the injury produced a predominant loss of plasma, as in burns, muscle ischemia or crush, peritonitis or clostridial myositis. Little or no evidence of a generalized increase in capillary permeability was found on examination of the rates of disappearance from the blood stream of dyes that attach to plasma albumin[16, 18, 19] or in experimental studies of transfer of tagged plasma proteins or sodium across the capillary membrane.[28-30]

Since the hematocrit is normal or low in most cases of wound shock,§ the condition may be considered to be due to whole-blood loss complicated by the other effects of the wound.

Neurogenic factors. The influence of afferent nervous stimuli in the pathogenesis of shock due to wounds has been hard to assess. Any wound, visceral manipulation or emotional stress may elicit a reflex reduction in arterial pressure (once called "primary shock"), usually accompanied by a reduction in pulse rate and sometimes by fainting.[24, 31, 32] In the absence of significant blood loss, recovery is spontaneous in the horizontal position. Studies by cardiac catheterization indicate that the syncopal hypotension that accompanies small venesections, or the anticipation of venesection, occurs while cardiac output and central venous pressure

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‡Earlier work has been reviewed by Blalock,[1] Harkins[2] and Wiggers.[3]

§The high red-cell counts observed in World War I were found in cutaneous blood samples taken after hours of exposure on cold battlefields and often did not represent the red-cell concentration of blood in active circulation.[33]

are normal, and is presumably to be attributed to arteriolar dilatation.[33] A similar hypotensive reaction has been observed in patients with stab wounds of the chest without extensive blood loss or tissue damage.[34] The possibility that such reflex effects contribute to the development of wound shock has been investigated intensively in animal experiments. Prolonged electric stimulation of autonomic depressor nerves in rabbits reduces arterial pressure but does not lead to progressive circulatory deterioration.[35] Similar stimulation of somatic afferent nerves (sciatic) in rabbits or dogs rarely produces more than a mild transient reduction in arterial pressure — more often the arterial pressure rises.[35, 36] But such stimulation diminishes the degree of blood-volume reduction required to cause lethal hemorrhagic shock,[36] and this may be interpreted as indicating a harmful effect of excessive vasoconstriction in hemorrhagic shock. The effect of deafferentation before limb trauma is disputed. The protection found by Swingle and his co-workers[37] is attributed to reduction in fluid loss by Phemister and Laestar,[38] who observed that equal or greater trauma to the normally innervated limb *fails* to produce shock if fluid loss is reduced by ligation of arteries to the injured area. The experiments of Phemister and Laestar also suggested that a toxic factor from the injured tissue was not important, because shock occurred only when a significant reduction in blood volume was produced. More recently, Wang et al.[39] re-examined the contribution of the neurogenic factor, having observed in dogs that 50 per cent mortality was attained after hind-limb trauma at an average residual blood volume of 73 cc. per kilogram of body weight but not after hemorrhage without trauma until the residual blood volume was reduced to 59 cc. per kilogram of body weight. They succeeded in restoring dogs to good health after extensive dorsal-root section and found that these animals survived trauma that was lethal to control dogs. The deafferentated traumatized dogs died only when the blood volume was further reduced to the degree that kills in simple hemorrhage experiments.[40] These authors consider, therefore, that they have demonstrated an added deleterious effect of sensory stimuli from the wound, which they believe operates by exaggerating the vasoconstrictor response, reducing peripheral blood flow by reduction in the caliber of the blood vessels and increase in the relative viscosity of the blood.[41]

Toxic factors. Failure to appreciate the full extent of blood and plasma loss into as well as from the site of injury led to a strong emphasis upon "toxic factors" in the studies of World War I. In general, these "toxins" were considered to be breakdown products of endogenous protein. Subsequent experimental work has shown that many substances of widely varied chemical nature, found in tissues or elaborated by bacteria, may produce circulatory collapse upon injection into intact animals.[42-56] Evidence sufficient to relate the development of wound shock to the release or elaboration of such substances in the area of injury is lacking, however. In all but exceptional instances among the cases studied blood-volume reduction is sufficient to account for the development of shock. The uniform responsiveness of wounded or burned men[57] to adequate blood-volume replacement further diminishes interest in possible toxic factors, except when overt sepsis supervenes or perhaps in the very late stages of shock. Because patients or animals that have experienced nearly uncomplicated blood loss often seem in better circulatory state and general condition than those that have suffered the same degree of blood loss as a result of extensive burns or crushing wounds, the impression persists that damaged tissue introduces toxic factors. Neurogenic influences and the greater viscosity of the blood in these high-hematocrit forms of shock may account for the differences.[58] It is likely, however, that infection also plays a role well before the signs of inflammation are apparent.[59]

Work with dogs has intensified interest in bacterial factors[47, 60-65] because the tissues of the dog always contain clostridia.[66] Even in the dog, however, muscle trauma or tourniquet release may not produce shock if plasma loss is prevented or promptly replaced.[67-69] Blalock[15] had shown earlier that blockade of venous and lymphatic return from the injured hind extremity does not prevent the development of shock. Prolonged cross circulation with a dog in shock due to hemorrhage or limb injury does not cause shock in a normal dog, if precautions are taken to avoid exsanguination.[70, 71]

Clinical Features

The observations of the recent period have disclosed no new signs or symptoms but have reaffirmed the usefulness of the standard clinical data. The level of the arterial pressure is a useful guide to the severity of the blood-volume deficiency. When the arterial pressure has dropped below 100 as a result of blood loss, the blood-volume deficiency is 30 per cent or more. The pulse rate is usually rapid but may be normal or even slow. The pulse volume, however, is always reduced. The face is pale, and the skin of the extremities is cold and usually moist when blood-volume reduction is sufficiently severe to produce a fall in arterial pressure. Delay in the refilling of skin vessels blanched by pressure is evidence of sluggishness of the peripheral circulation. Mottled cyanosis of the skin of the extremities is a sign of severe shock. The volume of injured tissue in a wound of the extremities or a burn gives a good indication of the probable degree of blood-volume deficit.[23, 24] Inadequacy of renal blood flow is manifested by oliguria or anuria, but this may not be recognized unless the patient is catheterized and the urine flow rate determined. The surgeon at the operating table becomes aware of the development

of shock by the reduction in capillary bleeding and darkening of the venous blood.

Since shock must ordinarily be treated without the aid of measurements of blood volume and cardiac output, it is fortunate that the clinical signs, and more particularly their trend, are reliable indexes of the deterioration of the circulation and of the adequacy of replacement therapy. When hematocrit values are high, the elevation in peripheral resistance due to increased blood viscosity tends to sustain arterial pressure levels as the cardiac output fails. In such circumstances the level of arterial pressure may lead to a deceptively favorable estimate of the state of the circulation.

Pain is not a prominent symptom of severely injured men in shock.[10] Almost all complain of thirst, however, which is alleviated only by restoration of blood volume.[10] Among the clinical observations of interest is the infrequency of shock among patients with head injury.[72]

Hemodynamics

Richards and his associates[18, 26, 73] substantially advanced the clinical description of the hemodynamic disturbance by measuring central venous pressure and cardiac output. In civilian patients in shock due to hemorrhage or skeletal trauma, at mean arterial pressure levels of 50 to 70, blood volume was found to be reduced by 35 to 40 per cent or about 2 liters, pressure in the right atrium by the equivalent of about 25 mm. of saline solution, and cardiac output to an average value of 2.0 liters per square meter per minute. The hematocrit was reduced by 33 per cent or more. Arterial pressure tracings showed a rapid collapse in diastole, associated with the decreased stroke volume. Although pressure in the right atrium was uniformly low, pressure in superficial arm veins was not always reduced; this was taken as evidence of venoconstriction. (Increased respiratory effort that reduces intrapleural pressure also reduces atrial pressure, and by producing collapse of the veins as they enter the thorax tend to delay the emptying of peripheral veins and to increase the venous pressure gradient.[74]) In shock caused by skeletal trauma, arterial pressure and cardiac output declined proportionately so that the calculated total peripheral resistance remained unchanged. After hemorrhage, however, vasoconstriction was apparently more active, for arterial pressure and peripheral resistance were higher in proportion to the decline in cardiac output. In burned patients the total peripheral resistance was very high. Increased blood viscosity undoubtedly contributed largely,[58] but vasoconstriction must have played a part as well,* for high peripheral resistance was observed in 2 patients studied soon after the burn, before hemoconcentration had occurred.[18] Brannon and his associates[77] subsequently applied the same technics of study to 8 patients in shock due to hemorrhage and confirmed the observations of the Richards group.

These observations in man agree in general with the extensive hemodynamic studies in dogs summarized by Wiggers.[8] Gregersen et al.[78, 79] point out that the vasoconstrictor response to hemorrhage and to trauma is greater in the dog, and that in the dog the constrictor response is greater to trauma than to hemorrhage, the reverse of the findings in patients.

Apart from evidence of vasoconstriction involving skin and kidneys, there is little information on the distribution of blood flow to individual organs of patients in shock. Because of limitations in technics for measuring blood flow, this information is incomplete in animal studies as well.

The terminal vascular bed has been beyond the range of systematic examination in human subjects during shock. Animal studies employing radioactive red cells or dyed plasma show that the circulation time is prolonged in shock almost entirely because of slowed flow in the systemic circuit. The pulmonary circulation time is about normal.[80, 81] Gibson et al.[82] showed in dogs that red cells and plasma are relatively stagnant within the capillary bed in advanced hemorrhagic shock, and may be restored to active circulation when transfusion therapy improves flow. Direct observations of the capillary bed of the mesentery and omentum of the dog by Shorr[83] and Zweifach and his associates[84-86] disclosed that in the early phase of hemorrhagic shock hyperactivity of precapillary sphincters results in a relatively empty capillary bed and blood flow channeled into the single "preferential" capillary leading most directly from arteriole to venule. In later phases diminished vascular tone leads to progressive stagnation of blood within widened capillaries.

General Pathology

In oligemic shock the tissues are relatively bloodless and dry. When death occurs in spite of blood replacement, visceral capillaries are diffusely congested and serous surfaces are moist.[87] Mallory et al.[25, 88] discuss the difficulty of assigning a specific histologic pattern to shock. In post-mortem examination of soldiers who survived at least eighteen hours, fat vacuoles were observed in the cardiac muscle fibres, the central cells of liver lobules and the ascending loops of Henle in the kidney. The doubly refractile lipoid of the adrenal cortex was depleted. Of interest was the very high incidence† of pulmonary fat embolism, once considered a cause of shock.

Little was seen in the histologic examination of these young men that would not be expected to

*Pressor substances may be demonstrated in the blood of burned animals.[75, 76]

†Pulmonary fat embolization was found in 65 per cent of Mallory's autopsies. Grant and Reeve[46] report pulmonary fat emboli in all autopsies after limb injuries, and renal and cerebral fat embolization in 50 per cent of these. Pulmonary fat embolization was also found in 80 per cent and renal and cerebral fat embolization in 20 per cent of autopsies after abdominal injuries.

return to normal upon recovery from shock. In the older civilian population, antecedent vascular disease and superimposed intravascular thrombosis may produce localized tissue necrosis, even when the general circulation responds to therapy. Clinical evidence of cerebral thrombosis is not uncommon among older patients who have experienced shock as a result of hemorrhage, trauma or surgery. The precipitation of coronary thrombosis by shock is well documented.[89, 90] Thrombosis of vessels of kidneys, intestines, lower extremities[91, 92] and retina[93] and thromboembolism[91, 94] are less often described but undoubtedly occur.

Metabolic and Biochemical Effects

Oxygen consumption of the quiet patient in shock is usually somewhat reduced, although restlessness or increased respiratory effort may raise the oxygen consumption to normal basal levels.[18, 77] Arterial blood remains normally oxygenated throughout the course of shock, but total oxygen transport to the tissues is reduced because of the decrease in cardiac output (and in hemoglobin concentration if hemodilution has occurred). Tissue anoxia is evident in the abnormally low oxygen content of venous blood and in the increasingly anaerobic pattern of carbohydrate metabolism.[18, 25]

Blood lactate and pyruvate concentrations rise, and the ratio of lactate to pyruvate increases late in shock.[95-98] The blood sugar concentration rises early, but falls as liver glycogen stores are depleted and may drop to very low levels. Catabolic changes in the tissues become manifest in increasing concentrations of inorganic phosphate, sulfate, potassium and amino acid nitrogen in the blood.[96] Unidentified fixed acids also appear.[95] In the absence of renal excretion, the accumulating fixed acids produce an increasing acidosis. Blood pH values may fall to 7.1 or lower. Pulmonary ventilation increases, and blood bicarbonate falls. Some of the amino acid is converted to urea, which is also retained in the blood stream. Blood and tissue ammonia levels likewise increase. Blood uric acid concentration rises in hemorrhagic shock in the dog,[99] but not often in clinical shock.[25] Less is known about disturbances in fat metabolism. Transfusion therapy in experimental hemorrhagic shock usually accelerates oxygen consumption[100] and restores the ability to clear blood lactate, pyruvate and amino acid nitrogen, even if recovery does not follow.[98, 101] It has not been demonstrated that this means a return to normal metabolic pathways. The elevated blood amino nitrogen level is usually not corrected if transfusion fails to effect recovery.[101]

Within the tissues the high energy-containing phosphate compounds diminish in concentration during shock.[102] In liver and kidney particularly, glycogen and adenosine phosphates tend to disappear whereas inorganic phosphate and lactic acid accumulate. The phosphocreatine of muscle becomes hydrolyzed. Many enzymatic disturbances in shock are known.[103-107] An increase in plasma peptidase activity has been found, and inhibitors of amino acid oxidase and of lactic dehydrogenase appear in the plasma. The fibrinolytic activity of the plasma is markedly increased.[108] Cocarboxylase of skeletal muscle is split during shock.[109] In the liver, however, the concentrations of both cocarboxylase and thiamine increase during shock.[109] Cozymase and alloxazine denucleotide activity of brain, muscle and, less often, of liver diminish in experimental hemorrhagic shock. The uptake of iodine by the thyroid gland is diminished in tourniquet shock in the rat.[110] Little is known of the pattern of biochemical repair after blood replacement.

Effects of Shock on Individual Organs

The effects of shock on individual organ systems have been studied to determine whether specific sites of damage prevent a favorable response to transfusion therapy and whether therapy directed toward individual critical organs may help to preserve the responsiveness of the patient as a whole.

Central nervous system. Considering their sensitiveness to total anoxia, cells of the central nervous system tolerate severe ischemia surprisingly well. Consciousness is retained and medullary centers continue to function throughout the course of shock. Brain damage of the kind observed after a few minutes of asphyxia or cardiac arrest is uncommon even after hours of severe shock. Men in mild or moderate shock tend to be restless and apprehensive, and those in deeper shock are more apathetic, although still aware of minor sensory stimuli.[10, 24] Brain tissue from animals in shock oxidizes normally in vitro and shows no defect in enzyme systems.[111-113] However, electroencephalographic studies in unanesthetized rabbits during hemorrhagic hypotension demonstrate slowed wave frequency and diminished amplitude, which are rapidly corrected by transfusion in "reversible" shock, but not corrected even while the arterial pressure is improved by transfusion in "irreversible" shock.[114]

Heart. In shock due to wounds and hemorrhage, the reduction in cardiac output is secondary to a failure of venous return.[8, 18] Observations in dogs indicate that coronary flow is reduced in proportion to the reduction in aortic pressure, but remains adequate for the reduced work load of the heart in shock.[8, 115, 116] Histologic examination at death after eighteen to twenty-four hours or more of shock disclosed fat vacuoles in the myocardial fibers of wounded soldiers[88] and of dogs subjected to hemorrhage or trauma, which also showed scattered foci of necrosis in heart muscle.[117] The respiration of heart-muscle slices taken from rats in hemorrhagic shock or tourniquet shock is diminished.[118, 119] However, in spite of these evidences of myocardial damage during prolonged shock, transfusion, which restores venous return and venous filling pressure,

restores cardiac output and arterial pressure.[8, 18, 120] Coronary blood flow in dogs improves after transfusion in proportion to the increase in arterial pressure.[115, 116, 121, 122] Analysis of atrial pressures in relation to cardiac output during severe hemorrhagic shock in the dog gives evidence of diminished strength of myocardial contraction,[8, 123, 124] but there is no reason to believe that myocardial weakness accounts for failure of healthy young men to respond to blood replacement. In patients with coronary arteriosclerosis, however, already limited coronary blood flow may drop below critical levels for myocardial viability, or thrombosis may be precipitated within diseased coronary vessels.[89, 90] Electrocardiographic evidence of myocardial ischemia is rarely found even during severe shock in wounded young men[125] or in laboratory animals,[126] but is frequently observed after hemorrhage in elderly patients.[127, 128]

Lungs. In the absence of injury to the respiratory apparatus, shock produces no demonstrable impairment in pulmonary function. Arterial oxygen saturation is normal until respiration ceases at death. Ventilation is usually increased, in consequence of acidosis and hypotension, and the carbon dioxide pressure in alveolar air and arterial blood is reduced.[18, 95] Acapnia, in turn, has long been considered to contribute to the reduction in venous pressure and flow,[129] and has more recently been shown to reduce cerebral blood flow in man,[130] perhaps contributing to apathy.

Liver. The liver may be expected to be severely handicapped in shock since a large part of its blood flow and oxygen supply is venous. Hepatic venous blood flow and oxygen saturation are sharply reduced during hemorrhagic shock in the dog[131] and presumably in man. The elevations in plasma levels of amino acid nitrogen, lactic acid and ammonia are attributable, in part at least, to inadequacy of hepatic function.[96] Hepatic tissue may become completely depleted of energy-containing organic compounds during severe shock.[102] Regeneration of plasma albumin,[132] prothrombin[133] and fibrinogen[134] are delayed or cease during shock. In view of the rapidity with which histologic signs of central necrosis may appear in the human liver — that is, during the course of an operation[135] — its inconstant presence at death in shock[88, 136, 137] is perhaps surprising. The presence of hepatic necrosis does not correlate with "reversibility" or "irreversibility" of experimental shock.[138] Nor does impairment of ability to clear injected bromsulfalein correlate with the presence or degree of shock due to battle injury[25] or gastrointestinal bleeding.[139] In experimental hemorrhagic shock, galactose tolerance may be reduced while bromsulfalein clearance is normal.[140] Plasma bilirubin levels may be elevated after extensive injury or operation with or without shock, especially if large hematomas are present or many transfusions have been given.[25, 135] Thermal trauma to erythrocytes may contribute to the development of jaundice in severe burns. Severe hepatic insufficiency due to parenchymal damage or bile-duct obstruction can predispose to shock.[141]

The development of overt hepatic insufficiency as a consequence of shock and its persistence as the cause of death after recovery from shock must be a rare clinical experience. In experimental work a number of special relations of the liver to the development of "irreversible" shock have been disclosed and are described in that connection.

Kidney. Renal blood flow is sharply reduced during shock, and urine formation ceases when the arterial pressure falls below 60 to 80.[99, 142-144] The reduction in renal blood flow is proportionately greater than that in cardiac output, indicating severe vasoconstriction. At a blood-volume loss of some 40 per cent renal blood flow may approach 0, even while arterial pressure is at 80 to 100.[145] Renal vasoconstriction usually persists for some time after transfusion has restored cardiac output and arterial pressure.[145, 146] Renal venous blood is not increasingly deoxygenated at low flow rates.[147] The kidney appears to be unique in this respect. Studies on human subjects[148] indicate that this is not due to the by-passing of cortical nephrons described by Trueta.[149] When urine flow has been restored after a period of shock, clearance studies indicate persisting tubular injury.[146]

In the Italian Theater of Operations it was noted that severely injured men, after recovering from shock, might continue to excrete little or no urine. The arterial pressure often rose to hypertensive levels, and, as anuria or severe oliguria persisted, blood chemical changes typical of uremia developed.[25] The urine collected was reddish, contained albumin, pigment and granular casts, was of fixed specific gravity and low acidity and, within the first few days of injury, gave a positive benzidine reaction after centrifuging. As uremia progressed, acidosis and twitching became marked, and central-nervous-system depression deepened into coma. Nearly all patients in whom post-traumatic anuria or severe oliguria developed died, usually within ten days. If fluids were forced in an effort to attain a diuresis, earlier death in pulmonary edema was usually produced.

The kidney at post-mortem examination disclosed a combination of lesions to which the name "lower-nephron nephrosis" has been given.[25, 150-152] This is a focal lesion confined to the thick limb of Henle and the distal convoluted tubule. The earliest change noted was lipoid degeneration, which usually made its appearance within eighteen hours of injury. A hemoglobin-like pigment within the lumen of convoluted and collecting tubules was a striking but inconstant finding. Tubular cells and sometimes large segments of the wall of the tubules showed degenerative changes or became necrotic. The neighboring interstitial tissue was edematous

and infiltrated with histiocytes and lymphocytes. Veins adjacent to necrotic tubules became thrombosed. Healing occurred by regeneration and by scar formation.

The same lesion is observed after hemolytic transfusion reactions, black-water fever, crush injury, sulfonamide intoxication, thermal burns and poisoning by mushrooms or carbon tetrachloride. The chief pathogenic factors in injured men are considered to be renal ischemia due to shock and hemoglobinemia or myoglobinemia.[153] Massive transfusion therapy increases the opportunities for intravascular hemolysis. Vasoconstriction produced by the stroma of hemolyzed red cells contributes to renal ischemia.[154] Attempts to alkalinize the urine in the hope of preventing this complication were ineffective and dangerous.[25, 155] The possible contribution of sulfonamides was hard to assess in the Italian campaign, but post-traumatic anuria is currently a serious problem in men injured in Korea who have not received sulfonamides. Dehydration before injury is considered to be a factor in the Korean casualties.

It is of interest that persistent renal dysfunction leading to death in uremia does not occur in dogs that survive shock, no matter how severe and prolonged the shock period may have been.[99, 158] Total clamping of the blood supply of the kidneys for four hours or more is required to cause permanent damage in the dog,[156] and the lesion so produced is necrosis, not lower-nephron nephrosis. The typical lesions of lower-nephron nephrosis may be obtained in the dog, however, by a combination of renal ischemia and intravenously injected methemoglobin.[157]

Note may be made of experimental studies indicating that the kidneys respond to shock by the secretion of at least two substances that may have a compensatory effect upon the circulation. A renal vasoexcitor material (VEM)[83] secreted early in shock is said to increase the tonus of arterioles and precapillary sphincters. Later in shock the secretion of VEM ceases.[84] Renin is an enzyme that is reported to act upon a plasma protein (hypertensinogen) to form a dialyzable pressor substance (hypertensin or angiotonin) that also increases cardiac output. Renin is secreted in response to hemorrhage, but the formation of hypertensin is limited by the failure of the liver to produce hypertensinogen.[158, 159] Furthermore, responsiveness to hypertensin is lost as shock progresses, and experimental "irreversible" hemorrhagic shock cannot be corrected by continuous or intermittent infusion of hypertensin.[160, 161]

Adrenal cortex. In the absence of direct measurements of adrenocortical secretion, evidence of response to injury has been found in the characteristic metabolic response, depression of circulating eosinophil count, increased excretion of ketosteroids and corticoids in the urine and histologic changes in the adrenal cortex at death.[9, 162-168] A reduction in cortical lipoid is usually observed in adrenal glands from patients who have died in shock.[25, 169] In rats subjected to trauma or graded hemorrhage, the total lipoid, cholesterol and ascorbic acid of the adrenal cortex are depleted.[170, 171] If severe bleeding is carried out abruptly, however, rats or dogs may die in irreversible hemorrhagic shock, with little or no observable reduction in total lipoid or in carbonyl-containing lipoid of the adrenal cortex.[172, 173] This may be a consequence of the abrupt reduction in adrenal blood flow.[174] Preliminary bioassays of adrenal venous blood in dogs so bled disclosed no increase in corticoid secretion during hemorrhagic shock.[175] These observations are being extended by chemical assay of adrenal venous blood.[176] The adrenal cortex of the dog that dies in hemorrhagic or traumatic shock shows congestion, hemorrhagic extravasation, degenerative cellular changes and infiltration with polymorphonuclear leukocytes.[173, 177-180] Similar changes are seen in the adrenal glands of patients dying of severe systemic infection.[169, 181]

Gastrointestinal tract. The mucosa of the stomach and intestinal tract of patients in shock may develop extensive and severe congestion and ulceration.[182-184] Observations in dogs disclose increased motility of the colon,[185] delayed absorption of water and isotonic glucose solution from isolated loops of small intestine but no delay in the absorption of physiologic saline solution,[186] and surprisingly good absorption of orally administered antibiotics.[187] Nevertheless, in man, oral therapy during shock is probably not to be relied upon.[188] Little is known of the level of secretory activity of the digestive glands during shock.

(To be concluded)

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MEDICAL INTELLIGENCE

FETAL RISKS FROM RUBELLA DURING PREGNANCY*

THEODORE H. INGALLS, M.D.† AND NATESAIER PURSHOTTAM, M.B., B.S.‡

BOSTON

ABOUT a year ago[1] readers of this column who practice obstetrics were requested to write to the editors giving certain basic data pertaining to rubella contracted during pregnancy. Subsequently, reports were made of the condition of the baby. The task was undertaken to determine the risks of death or deformity for the developing fetus. A number of physicians have responded by sending the desired information concerning 19 cases. Similar studies[2-6] have previously been published although each series involves such a small number of cases that the only possibility of determining over-all risks is by pooling of data.

The desiderata for a prospective type of inquiry have been reviewed by Logan[7] and can be summarized as follows: selection of each case should be made before the child is born; the inquiry should include cases of rubella (or other virus infection) occurring at all stages of pregnancy from the earliest weeks; the diagnosis should be made by a medical practitioner; the outcome should be recorded whatever its nature; and, ideally, a control series should be included in which the infection studied did not occur during pregnancy.

A prospective investigation adhering to these criteria is yet to be done, but in the meanwhile, enough evidence is available for re-examination of the risks of rubella according to trimester of pregnancy and for a report on the findings of the past year's study.

Collection of an adequate number of cases and analysis of the multiple effects of rubella during gestation are beset with too many difficulties to be successfully accomplished by any one physician. This particular complication is rare, and moreover it is difficult to detect and classify all defects of the surviving infant even when it is born alive and externally well. The successful completion of a collective effort demonstrates the possibility of making some headway against such odds when physicians co-operate and help centralize their data in some manner, as in the present venture.

It is now well known that rubella takes its toll on the developing embryo, as measured later by death or deformity of the fetus, especially when the infection occurs during the first trimester of pregnancy; but a critical question still to be satisfactorily answered is, What is the risk of such infection at different stages of gestation? The 19 cases of rubella occurring during the first and second trimesters of pregnancy may be added to experience reported by previous investigators even though the ideal prospective study, as indicated above, is still to come.

TABLE 1. *Rubella and Outcome of Pregnancy.*

SOURCE OF DATA	NO. OF CASES	1ST TRIMESTER			2D TRIMESTER			3D TRIMESTER		
		TOTAL BIRTHS	STILL-BIRTHS	CONGENITAL DEFECTS	TOTAL BIRTHS	STILL-BIRTHS	CONGENITAL DEFECTS	TOTAL BIRTHS	STILL-BIRTHS	CONGENITAL DEFECTS
Grönvall & Selander[5]	28	13	2	0	13	1	1	2	0	0
Aycock & Ingalls[3]	4	2	0	1	1	0	0	1	0	0
Fox & Bortin[2]	12	9	1	1	1	0	0	2	0	0
Hill & Galloway[6]	9	5	1	0	2	0	0	2	0	0
Present series	19	13	0	1	6	1	1	0	0	0
Totals	72	42	4 (9.5%)	3 (7%)	23	2 (9%)	2 (9%)	7	0 (—)	0 (—)
Ober, Horton & Feemster[4]	52	22	7 (32%)	4 (18%)	20	1 (5%)	0 (—)	10	2 (20%)	0 (—)

The data presented in Table 1 indicate a risk of losing the conceptus in less than 10 per cent and of producing defective infants in 7 per cent of cases when rubella occurs in the first trimester of pregnancy and a similar loss of 7 per cent and 6 per cent in the second. All such studies suffer from a paucity of data for the third trimester, though the indications are that the risk of fetal death or defect is negligible during this period (Table 1).

The report of Ober, Horton and Feemster[4] has been allowed to stand by itself in Table 1 because, in this study, 3068 women who were reported to have suffered from rubella were reached by questionnaire, and of the 1164 who replied, 49 were found to have suffered the infection in the course of pregnancy. Valuable as such data are they are omitted from the analysis since there was room for an undetectable but significant factor to operate in determining women who replied and those who

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did not reply to the questionnaire. For these reasons and also because the risk quoted, 50 per cent for first-trimester infection, 10 per cent for the second and 20 per cent for the third, is so different from subsequent inquiries, this study is listed separately.

If the present series is pooled with those of other investigators, the total risk of stillbirth or deformity is about 17 per cent for infection in the first and about 12 per cent for infection in the second trimester.

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A FRAGMENT FROM SIR THOMAS BROWNE

Henry R. Viets, M.D.

BOSTON

SIR Thomas Browne, having studied medicine in Montpellier and Padua, graduated, M. D., at Leyden and received the same degree from Oxford University in 1637. Thus well trained in academic medicine, he settled in Norwich to practice physics and to raise his large family, believed to have consisted of 7 daughters of whom the best known, Elizabeth, probably the third, was born about 1648. His son, Edward, became a physician and author.

Like many girls, Elizabeth kept a Commonplace Book. She appears to have been a serious-minded person, devoted to her scholarly father and, according to Keynes,* of help to him "in the accumulation of the laboured stores of erudition with which his works are packed." Since both the *Religio Medici* (1642-3) and the *Pseudodoxia Epidemica* (1646) were published before Elizabeth was born and *Hydriotaphia: Urn burial* (1658), when she was only ten years of age, her help must have come in the preparation of the later editions and the numerous translations of the *Religio*, for this famous book was to appear in Latin, Dutch, French and German. Of importance may have been her literary contribution after her father's death in 1682, for his posthumous work, *Christian Morals*, published at Cambridge in 1716, contains a short prefatory note by her.

The Commonplace Book, kept by Betty Browne, before her marriage to George Lyttelton in 1680 and her moving with her husband to Guernsey in 1681, is of the usual type, with extracts from poets, some prose fragments, religious aphorisms and verses. Its value lies in the few personal items and one fragment of prose written by Browne in his best manner. A list of books read to her father by Betty "at nights" is given. As Keynes notes, "the brain reels in the perusal of it" — *all Plutarks liues*, fol.; *all the Turkish historie*, fol.; *all Baker's Cronicle of England*, fol.; *all ye history of China by Semedo*, fol.; *all fox his book of Martyrs*, fol.; *all the historie of Naples*, fol. and many others. (Heavy reading for a girl in her early thirties during those long nights!)

But of more interest is a brief bit of prose by Thomas Browne, not preserved anywhere except in the present volume, edited by Keynes, and never before printed. It was presumably copied by Elizabeth Lyttelton from her father's writings and afterward completed at his dictation. It is a noble tribute to the most merciful executioner of death, tuberculosis, "wherein a man is Led, not torn, unto his transition." The passage is printed by Keynes exactly as it stands, except that punctuation has been supplied:

Sir Thomas Browne, from a drawing attributed to David Loggan.

> Many haue thought it no Lost time to exercise their witts in the Praises of disease, some haue wittyly Commended baldness, others extolled quartane agues and some haue left incomiums of the Gout and think they extenuat the anguish of it when they tell what famous men, what Emperours and Learned Persons haue been severe examples of that disease and that it is not a disease of fooles, but of men of Parts and sences; but none haue attempted the incomium of Consumptions, which haue so well deserved as to this and the other world, giueing a Mercifull Conclution to the one, a solem preparation to the other: he that Prays against tormenting diseases or sudden death hath his Littany heard in this disease, which is one of the Mercyfullest executioners of Death, whose blows are scars to be felt, which no man would be killed to be free of, wherin a man is Led, not torn, unto his transition, may number his dayes and even Last hours and speak unto his Saviour when he is within a moment of him.
>
> by T. B., M.D.

**The Commonplace Book of Elizabeth Lyttelton, daughter of Sir Thomas Browne.* Description by Geoffrey Keynes. 34 pp. Cambridge: University Press, 1919. P. 6.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39371

PRESENTATION OF CASE

A sixty-three-year-old man was admitted to the hospital because of pain in the right flank and hematuria.

The patient was well until sixteen months before admission, when he was admitted to the hospital with lobar pneumonia. He was treated with penicillin and chloramphenicol, but recovery was slow. He was discharged at the end of two weeks, when his lung was clear except for slight residual scarring. Four weeks later, when he visited his physician, the hemoglobin was 9.8 gm. whereas in the hospital it had been 12.5 gm. per 100 cc. He was advised to return for investigation of the anemia but refused, and treated himself with iron. One month later his secretary informed his physician that the patient was not gaining strength. However, when the physician called the patient, the patient said that he felt well, and refused further study. Six months before entry weakness, anorexia and restlessness at night developed; these symptoms had persisted. Six weeks before admission he fell on the side of the bath tub and was said to have fractured the fifth, sixth, seventh and eighth right ribs. Anorexia and weakness continued, and ten days before admission he began to have hematuria. For the past three or four days he had noted some pain in the right flank that was aggravated by lying on the right side. He also had nocturia (four times) and some burning on urination. He had lost about 45 pounds of weight since the bout of pneumonia and said that he had not felt "right" since then, although he did not have cough or hemoptysis.

Physical examination showed a poorly nourished man who appeared chronically ill. There was evidence of weight loss. The lungs were clear; the heart was normal except for a Grade 1 apical systolic murmur. The abdomen was large, with a slightly nodular, firm to hard, nontender mass filling the right upper quadrant and extending almost to the umbilicus. It moved with inspiration and could be moved readily with the examiner's hand in the right costovertebral angle. The spleen was not felt. The rest of the examination was negative.

The temperature was 98°F., the pulse 90, and the respirations 20. The blood pressure was 135 systolic, 70 diastolic.

A urine specimen was cloudy brown, had a specific gravity of 1.018 and gave a +++ test for albumin; the sediment was loaded with red cells. The hemoglobin was 10.5 gm. per 100 cc., and the white-cell count 12,800, with 72 per cent neutrophils, 26 per cent lymphocytes and 2 per cent eosinophils. There was a slight variation in size of the red cells on smear; a reticulocyte count was 2 per cent. The prothrombin time was 18 seconds (normal, 14 seconds). The serum nonprotein nitrogen was 24 mg., the total protein 7.1 gm., the albumin 3.6 gm., the globulin 3.5 gm., the alkaline phosphatase 2.5 units, and the serum amylase 20 units per 100 cc. A phenolsulphonephthalein test showed 35 per cent excretion in two hours, but it was not certain that this test was satisfactory.

FIGURE 1. *Intravenous Pyelogram.*
Arrows point to right abdominal mass. The right kidney appears to be displaced laterally and upward. Contrast substance is present within the right renal pelvis.

A roentgenogram of the chest revealed some tortuosity of the aorta but was otherwise normal; there was no evidence of fractured ribs. On gastrointestinal series, the esophagus, stomach and small bowel were normal. The mass in the right upper quadrant displaced the descending limb of the duodenum anteriorly and medially. A barium-enema examination demonstrated that the mass displaced

the colon upward and anteriorly, but was not attached to it. After evacuation the transverse colon lay below the level of the mass. In an intravenous pyelogram the survey abdominal film disclosed a large ovoid mass occupying the right upper quadrant and extending below the crest of the ilium (Fig. 1). Through this mass, the psoas-muscle shadow and the renal shadow could be seen. The kidney appeared to be displaced upward; its lower pole was rotated laterally. The intravenous dye appeared promptly in the right kidney, and on serial films up to 60 minutes. The collecting system was displaced laterally so that its axis was more horizontal than normal. The renal pelvis and upper ureter were bowed outward, but there was no localized deformity of any portion of the collecting system. At no time did intravenous dye appear in the left kidney in sufficient quantity to outline the pelvis and calyxes. A bilateral retrograde pyelogram revealed that the right ureter was markedly displaced to the right side (Fig. 2). The left ureter occupied a position nearer the midline than is usually seen.

FIGURE 2. *Retrograde Pyelogram Showing Contrast Substance within the Right Renal Pelvis and Displacement of the Right Ureter Laterally.*

The left urinary collecting system is not visualized.

On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WYLAND F. LEADBETTER*: Although I have been over the protocol I have not as yet been able to arrive at a diagnosis that I think is satisfactory. I hope, with the help of more x-ray films, to arrive at some decision.

So far as I can tell the lobar pneumonia sixteen months before the patient came into the hospital had no bearing on the illness that we are considering. It does appear that the patient did not recover well, and his hemoglobin was low a month after he was discharged from the hospital. Apparently, he had a progressive illness, which at the end of a period of about fourteen months resulted in anorexia, weakness and lastly hematuria that occurred ten days before he came into the hospital. Also he had pain in the right flank. Nothing in the physical examination seems to have had a bearing on this matter except the presence of a right-upper-quadrant mass that was easily felt and was said to move with respiration. If a mass moves with inspiration, one assumes that the mass is not firmly fixed. This allows one to conclude that the mass is not inflammatory and, if a tumor, not a lesion that is infiltrating its capsule and surrounding tissue but probably is well localized and contained in its capsule. The position of the mass in the right upper quadrant, of course, calls for a considerable amount of diagnostic work to determine its nature. It was stated that the spleen was not felt. The urine contained many red cells but apparently did not contain pus, which is of some significance. I think most of the other laboratory data have no particular bearing on the case. The x-ray evidence seems to be most important and probably the basis on which a diagnosis can be made here. May I see the films?

DR. STANLEY M. WYMAN: The lungs seem clear and the heart shadow is not too unusual for a patient of this age. The films of the upper gastrointestinal tract demonstrate a considerable degree of displacement of the distal duodenum to the left, upward and, as one sees in the lateral view, anteriorly by the mass, which can be outlined. The mass extends up to and perhaps slightly across the midline. The films of the intravenous pyelogram show what can be taken for a left-kidney shadow; the kidney certainly lies much farther to the right than it should, its shadow coming down and then being lost over the spine (Fig. 1). The lower pole seems to be directed toward the large mass originally described. The collecting system of the right kidney is well seen; the calyxes are directed either forward or backward — one cannot tell — rather than laterally. The renal pelvis is lying far laterally, with the ureter coming down laterally to the kidney. The examination of the colon demonstrates a normal colon; after evacuation the transverse colon lies entirely below the mass. At this time the mass is quite well outlined and appears to extend beyond the midline. It is hard to be sure of any appreciable amount of dye, but there is a small density in the midportion of the mass just to the left of the spine that makes one wonder if there is some intravenous

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dye appearing in the left-kidney pelvis. The retrograde examination shows quite conclusively the location of the pelvis of the left kidney in the same region; the calyxes are directed quite unusually, a little more toward the midline rather than in a straight anteroposterior plane. On the right the ureter is well seen, and this confirms the original observation — namely, that the ureter lies very far laterally (Fig. 2).

DR. LEADBETTER: There is no mention of findings on cystoscopy. If it was examined I assume that the bladder was normal.

A PHYSICIAN: Yes, the bladder was normal. Blood was seen coming only from the left ureter.

DR. LEADBETTER: We have the problem here not only of deciding what the mass in the upper abdomen was but also why the left kidney was relatively nonfunctioning. The negative cystoscopy rules out a lesion in the bladder obstructing the left ureter. The fact that the catheter could be passed up the left side is further evidence that there was no obstructive phenomenon involving the upper urinary tract.

As a starting point I might say that we are dealing with a retroperitoneal lesion. The x-ray films clearly demonstrate the fact that the duodenum and bowel were displaced anteriorly. Any mass in this area can be considered in terms of a lesion of the kidneys, a lesion of the pancreas, an enlargement of the retroperitoneal lymph nodes such as one finds in metastases from testicular tumors, a vascular lesion such as an aneurysm, an abscess, a cyst or polycystic disease, hydronephrosis, tumor and of course any number of retroperitoneal lesions of a malignant or benign nature. In this case certain findings tend to call attention to the urinary tract — most important is the history of hematuria. By the intravenous pyelogram we know that the left kidney functioned little or none, that the right kidney was functioning, and the right ureter was displaced far laterally by the mass that filled the midabdomen. If we assume that the shadow visualized in the films in the left kidney area was the left kidney, I have to explain first how this kidney shadow was displaced or was positioned medially. Furthermore, the axis of this kidney was longitudinally aligned instead of lying in relation to the psoas muscle in an oblique fashion. The axis is almost vertical. Moreover, if one follows the outline of this kidney in the x-ray films it seems to cross the midline. That, under ordinary circumstances, would point to a horseshoe kidney. In this case it is not absolutely possible to trace this line of the kidney into the mass, but I am tempted to believe that it is continuous. I can rule out a hydronephrosis because a hydronephrosis under ordinary circumstances would probably displace the kidney to the left side. With a horseshoe kidney, however, the kidney is fixed so a hydronephrosis might present peculiarly but it is clear from the injection of dye (left retrograde pyelogram), which seems to have been fairly satisfactory, that hydronephrosis is ruled out. If we assume that it was not a horseshoe kidney, I have to determine what was responsible for the peculiar position of the kidney on the left side. It is possible that a nonrotated kidney, which is exemplified in some films by the structure here, since the pelvis is anterior, would result in a kidney located in approximately this axis, but I have really no evidence for or against that and rather doubt it. If I assume that the mass that was palpated in the upper abdomen was continuous with the left kidney I must also assume that I am dealing with a horseshoe kidney. The other possibilities are that this was a peculiarly formed kidney such as a cake kidney, and that it was a horseshoe kidney with a supernumerary kidney on the right side.

With the history of hematuria, the fact that at least some blood was coming from the left kidney since the cystoscopist reported blood coming from the left ureter, the relative absence of function of the left kidney and the absence of pus cells in the urine, I am obliged to make a diagnosis of a lesion of the left kidney that cannot have been hydronephrosis. It could have been tuberculosis, but I shall rule that out by virtue of the fact that there was no pus in the urine. It is more likely that there was a cystic change in the kidney or a tumor in the kidney. I cannot arrive at any definite diagnosis, but I think that we are dealing with some type of renal abnormality, probably a horseshoe kidney with a tumor or a large cyst involving the isthmus of the kidney. In view of the loss of weight and the hematuria I am inclined to believe that the patient had a tumor.

There are, it seems to me, few other considerations. I should point out that a mass in this area is common as a result of metastases to the paracaval or para-aortal lymph nodes from a testicular tumor. Occasionally, with other malignant lesions, enlargement of these nodes may produce a mass that could give rise to exactly the same picture except that it would not explain the relative nonfunction or the position of the left kidney. I have seen metastases from testicular tumors that have resulted in relative nonfunctioning of the kidney from compression of the artery and I have seen the kidneys return to function after x-ray therapy was given.

One could, I suppose, consider the possibility of lymphosarcoma or some unusual lesion, but I think that the difficulty in this man was a lesion of the kidney, possibly tumor.

DR. BENJAMIN CASTLEMAN: Dr. Point, you saw this patient; would you tell us your opinion?

DR. WARREN POINT: When I first saw this patient, the problem seemed to be quite simple; I thought he had a hypernephroma because of the large mass, bloody urine, weight loss and so forth, so I admitted him with that diagnosis. Then when

we took the x-ray films and the right kidney seemed at first to be perfectly all right, I changed my diagnosis to retroperitoneal sarcoma probably involving the left kidney and left ureter to produce the blood, with the largest part of the lesion on the right side. Dr. Kerr was asked to see the patient and did the surgery; perhaps he will tell us what he saw at operation.

Clinical Diagnosis

?Retroperitoneal sarcoma.

Dr. Wyland F. Leadbetter's Diagnosis

Tumor of isthmus of horseshoe kidney.

Anatomical Diagnosis

Renal-cell carcinoma of isthmus of horseshoe kidney.

Pathological Discussion

Dr. Walter S. Kerr, Jr.: First of all, I should like to congratulate Dr. Leadbetter on his excellent and complete discussion of the problem. We believed that the lesion, which was almost completely on the right side of the abdomen, explained the change in the position of the right kidney, and did not recognize it as a horseshoe kidney. The tumor was approached through a right thoracoabdominal incision. It was soon obvious that there was a horseshoe kidney and that the tumor arose from its isthmus. After the tumor was completely mobilized from the surrounding retroperitoneal structures, the isthmus was divided close to the right kidney, leaving a margin of approximately 5 cm. of normal tissue. An attempt was made to remove the left kidney with the specimen, but the large size of the tumor made this technically difficult and thus the isthmus was divided close to the left kidney, allowing the removal of the tumor. There was tumor thrombus in one of the left renal veins; this vein was opened, and the thrombus was milked out. Several of the other vessels of the left kidney were divided in the process of freeing up the tumor, and thus it was believed that the left kidney should be removed. However the removal of the left kidney through the left-sided incision proved to be technically very difficult, and in view of the duration of the operation and the condition of the patient, it was decided to postpone the nephrectomy on the left to a later date.

Dr. Castleman: This is a copy of a drawing that Dr. F. W. Garran made of the horseshoe kidney with the large tumor in the isthmus projecting upward and anteriorly (Fig. 3). The part lying in the center was removed, leaving both the kidney and ureters intact. The tumor proved to be a renal-cell carcinoma, or hypernephroma, on microscopical examination.

Dr. Leadbetter: I have recently seen a similar patient, who was not operated on with the diagnosis of tumor at all. When we exposed the kidney, intending to divide the isthmus, we found a renal-cell carcinoma of small size, which we could resect.

Dr. Castleman: Dr. Kerr, do you think you should remove the left side of the horseshoe kidney?

Dr. Kerr: Yes; we intend to do that. Most of the venous and part of the arterial supply of the left kidney has been divided. Tumor growing down into the venous drainage of that side was removed to permit the isthmus to be taken out.

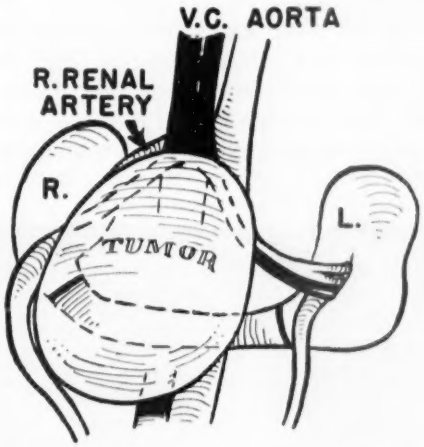

Figure 3. *Renal-Cell Carcinoma Involving Isthmus of Horseshoe Kidney.*
The tumor and the isthmus between the heavy black lines were resected at operation.

CASE 39372

Presentation of Case

First admission. A seventy-two-year-old retired Russian-born blacksmith was admitted to the hospital because of pain in the left anterior portion of the chest and fever for three weeks.

He had had a chronic cough, worse in the mornings, for many years that he attributed to smoking. The cough had become more severe in the last year. His family thought he had become much thinner. Two months before admission he had had an episode of hemoptysis, bringing up "chunks" of blood, but this had not recurred. Five weeks later a pleuritic type of pain in the left anterior part of the chest developed and was associated with malaise, anorexia, intermittent fever and sweats. His physician gave him sulfonamides and penicillin, which afforded transient improvement, but a rash developed and this therapy was stopped. The symptoms had persisted.

For the past ten years he had had episodes of anginal pain relieved by rest and nitroglycerin.

Electrocardiograms on two occasions five years previously had shown changes suggestive of old posterior myocardial infarction.

Physical examination revealed a well developed, slightly emaciated man with cyanotic lips and nails who appeared acutely ill. There was no clubbing of the fingers. The entire left aspect of the chest anteriorly and laterally was dull to percussion, and in that area the breath sounds were decreased in intensity and were bronchovesicular, with many coarse rales. The breath sounds were slightly diminished over the remainder of the chest, and the anteroposterior chest diameter was moderately increased. The left border of the heart lay within the midclavicular line; no murmurs were heard. The rest of the examination was negative.

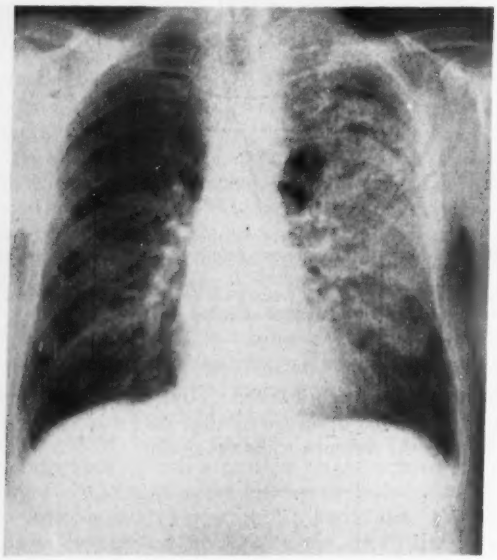

FIGURE 1.

The temperature was 102.4°F. by rectum, the pulse 88 and regular, and the respirations 28. The blood pressure was 140 systolic, 80 diastolic.

The urine was normal. A stool was guaiac negative. The blood hemoglobin was 13 gm. per 100 cc. The white-cell count was 12,800, with 89 per cent neutrophils, 9 per cent lymphocytes and 2 per cent monocytes. Two sputum cultures grew abundant alpha-hemolytic streptococci, and a few colonies of *Staphylococcus aureus* and *Neisseria catarrhalis*. Numerous blood cultures were negative; some grew diphtheroids.

Three smears for acid-fast bacilli were negative. A roentgenogram of the chest showed consolidation of the left upper lobe, with no pleural fluid present (Fig. 1). An electrocardiogram demonstrated changes suggestive of myocardial ischemia.

The patient was treated with aureomycin but continued to cough up large amounts of yellow sputum without blood. The temperature remained about 100°F., with occasional spikes to 102°F. The x-ray films of the chest remained unchanged. Cytologic examinations of the sputum at intervals were reported doubtful on five occasions, negative on two and unsatisfactory on two.

Bronchoscopic examination on the nineteenth hospital day revealed only a slight diffuse bronchitis.

Because of attacks of an anginal type of chest pain and dyspnea, digitalis was given, with slight improvement. Serial electrocardiograms disclosed changes suggestive of a posterior myocardial infarct. Cough productive of thick, tenacious mucoid material persisted. The patient continued to complain of extreme weakness and was anorexic.

A gastrointestinal series six weeks after admission demonstrated only a hiatus hernia of the gastric fundus.

His condition remained the same, and he was discharged on the seventy-sixth day on a low-salt diet and digitalis. After discharge, examinations of six guinea pigs that had been injected with sputum concentrate were reported negative for tubercle bacilli.

Second admission (about two months later). One month after discharge the patient was seen in the Out-Patient Clinic. He was feeling better but still had a severe productive cough. There were harsh breath sounds and rhonchi in the left side of the chest.

At the time of his next visit a month later he complained that the cough was more severe and more productive. There had been sharp pain in the right aspect of the chest four days previously, partially relieved by nitroglycerin. Three days previously a pleuritic pain developed in the left portion of the chest. Physical findings were unchanged. He was admitted for re-evaluation.

The urinalysis and blood count were unchanged. A roentgenogram of the chest showed little change from previous films, but the consolidated left upper lobe was questionably reduced in size. An electrocardiogram demonstrated changes consistent with

an old myocardial infarct. A sputum culture grew abundant *N. catarrhalis*, abundant diphtheroids and a few colonies of *Staph. albus*.

The patient was given Gantrisin, 1 gm. four times daily, and sedation. Digitalis was continued. He failed to improve, and on the fourth day he had a grand-mal type of seizure lasting a few minutes, followed by unconsciousness for five to ten minutes. Physical examination after the convulsion revealed a blood pressure of 130 systolic, 70 diastolic. The pulse was 130 per minute. The reflexes were generally hyperactive and equal except that the right knee jerk was ++++, and the left ++; the right ankle jerk was ++++, and the left +++. For fifteen minutes post-ictally there was right-ankle clonus. The plantar reflexes were extensor bilaterally.

Lumbar puncture thirty minutes after the seizure was negative. An electroencephalogram was mildly abnormal, with diffuse slow activity of 3.5 to 6 per second. One linkage suggested that this was more marked in the left temporal occipital region. An x-ray film of the skull was negative except for calcification of the internal carotid arteries.

Five days later neurologic examination showed a complete return to normal. More cytologic examinations of the sputum were performed and reported as one doubtful and three negative. Laminograms of the chest demonstrated the left-upper-lobe bronchus and its main branches clearly, and smaller bronchi could be traced well toward the lung apex without evidence of any obstructive bronchial lesion. Histoplasmin 1:1000 skin test resulted in a 0.64-cm. area of induration without redness at twenty-four and forty-eight hours; coccidioidin 1:1000 skin test was negative.

While on penicillin therapy the patient continued to run a low-grade fever (temperature of 100 to 101°F.). He had a severe productive cough and almost constant dyspnea, with a respiratory rate occasionally up to 40 per minute. He was discharged on the eleventh hospital day to continue penicillin therapy at home.

Final admission (twenty-six days later). He was re-admitted on the surgical service, where his condition was found to be unchanged except for a decrease in cyanosis.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Arthur S. Pier, Jr.*: This seventy-two-year-old man had had a cough for many years that had become much worse during the year before admission and productive of large amounts of sputum — sputum that apparently was either yellowish or thick, tenacious and mucoid. He had severe dyspnea, cyanosis and weakness and a slight fever and on the whole a progressive downhill course. He was followed for about five months in this hospital. Blood spitting occurred once and apparently did not recur. I wonder if we can see the x-ray films.

Dr. Joseph Hanelin: In the chest examinations made over a five-month interval the findings are fairly similar at all times (Fig. 1), only varying somewhat in the amount of consolidation in the left upper lobe with slight reduction in volume of the left upper lobe toward the end of the five-month period. The remainder of the left lung is clear. There is no increase in pleural fluid. There is no mediastinal shift, and the right lung has remained clear all through this period. The laminograms, which I have not included here, showed good patency of the left-upper-lobe bronchus.

Dr. Pier: Is there any evidence of tuberculosis on the right side or in either apex?

Dr. Hanelin: I do not see anything on the left side except the diffuse involvement of the left upper lobe and nothing in the right lung of any moment. There may be some calcified scars at the right hilus.

Dr. Pier: Was there any evidence of bronchiectasis in the laminograms?

Dr. Hanelin: I think the bronchi were somewhat dilated, but that was not a marked feature.

Dr. Pier: I think the backbone of this problem is whether a malignant process or a largely infectious process was the primary disease. As an infection alone I should consider tuberculosis, but a tuberculous process this extensive would be virtually a tuberculous pneumonia, and the physicians certainly should have had no trouble in finding acid-fast organisms in the sputum; therefore, with six negative guinea pigs, I think I can rule out active tuberculosis as the primary disease. When I first read the history I wondered whether the patient had an old tuberculous fibrosis in the left upper lobe that had caused scarring, bronchiectasis and a devitalized lobe in which secondary infection had started and led to a chronic low-grade pneumonitis with

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more bronchiectasis, abscess formation and more fibrosis. I do not think this suggestion is likely because the x-ray films do not show much contraction in the size of the left upper lobe or any clear-cut pulmonary fibrosis. The absence of bronchial dilatation is hardly consistent with a severe bronchiectasis. The laminograms apparently demonstrated quite normal bronchi. Furthermore, there is no good evidence that the patient ever had tuberculosis. There was no shift of the trachea or of the mediastinum as one would expect if he had a withered, contracted left upper lobe caused by old tuberculosis.

I wonder vaguely about an unresolved pneumonia involving the left upper lobe. The diagnosis of unresolved pneumonia is a dangerous one to make. I think an unresolved pneumonia lasting for five months usually turns out to be cancer, tuberculosis, lung abscess or a foreign body obstructing a bronchus. Also there was no clear-cut beginning for a pneumonia in this case; the whole process was very insidious. The patient did not have much fever or much white-cell response. He had no clubbing such as would go with a pneumonic abscess or bronchiectasis.

Passing next to the question of fungous infection, I think it is conceivable that he had actinomycosis. He was reported at times to have had yellow sputum. I should think that sulfur granules probably could have been found in the sputum, and that the organisms could have been grown on culture. Since there is no report of the finding of actinomyces I shall assume that he did not have actinomycosis. I shall assume also that he did not have a granulomatous process such as sarcoid or Hodgkin's disease, since the x-ray picture does not suggest either.

I wondered whether I could get any help from the convulsive episode — the sudden convulsion during the third admission resulting in a temporary hyper-reflexia on the right side. If I postulate a lung abscess or a severe bronchiectasis, I could guess at a metastatic abscess to the brain. If I postulate a lung tumor, he could have had a metastatic tumor to the brain. The convulsion, however, was not reported as being Jacksonian; he complained of no headache at any time; the eye grounds were normal; the neurologic signs completely cleared within a few weeks or a few days and there was no recurrence; the lumbar puncture was entirely normal as was the spinal-fluid pressure; and the spinal-fluid cell count was not increased as one would expect with an abscess. In short, there is no evidence for a space-occupying lesion. The patient could have had a cerebral hemorrhage, but there again I should have expected an increase in the spinal-fluid pressure, perhaps some blood in the spinal fluid, some headache and less rapid clearing of the symptoms and signs. I think the best explanation for the convulsive episode is a small cerebral thrombosis or a small cerebral embolus from a diseased heart. He had vascular disease and a long history of angina pectoris, and myocardial infarction was suspected. He also had calcified internal carotid arteries. I think an embolus to the brain or a small cerebral thrombosis produced the loss of consciousness and convulsion, and I do not believe I can hook it up with the pulmonary picture.

Passing on to cancer in the lung, one thinks, of course, of bronchogenic carcinoma. There is a good deal against a bronchogenic carcinoma here. First of all, bronchoscopic examination was negative for tumor, but since it is sometimes difficult to spot a tumor in the upper lobe by bronchoscopy this does not rule out bronchogenic carcinoma completely, although it is strong evidence against it. Next, and more important perhaps, the well outlined bronchi in the laminograms showed no obstruction either in the major bronchus or in the smaller bronchi and no upper-lobe collapse so that I think a squamous-cell or oat-cell carcinoma would be very unlikely. Finally, there was no definite positive cytologic smear. I asked Mrs. Ruth Graham, of the cytology laboratory, what she considered a whole series of doubtful smears to mean. I wondered whether it could occur in chronic pulmonary infection. She said that it could and that it might signify squamous metaplasia, which does not really help me a great deal, but I think the fact that so many smears were not positive is strong evidence against a bronchogenic or oat-cell carcinoma. A more peripheral tumor, like an adenocarcinoma, usually shows up as a well defined, rounded mass, and there was nothing very well defined here. I think the same argument about the cytologic smear applies to adenocarcinoma, which I therefore discard.

There is a peripheral type of tumor called an alveolar-cell carcinoma that is supposed to arise from the smaller bronchi and is known to infiltrate the air spaces of the lung and to give rise at times to a sort of carcinomatous pneumonia. Such a tumor would be perfectly consistent with this x-ray picture. I should expect a negative bronchoscopic examination, but I should certainly expect some positive

cytologic examinations because the alveoli and bronchi would be literally loaded with tumor cells.

I think the disease that best fits this picture, although there are one or two unusual features, is a rare condition called pulmonary adenomatosis. Being a rare disease, it constitutes a risky diagnosis. Pulmonary adenomatosis is usually multicentric in origin. Here one lobe was definitely involved, but I think that in this lobe the process looked as if it were multicentric in origin, with scattered areas of fuzzy density. I do not see any disease in the right lung in the films, but the nodules, when they are very small, are not always visible in the x-ray films, and they may be tiny in the beginning. Pulmonary adenomatosis is a disease of unknown origin and has a benign histologic appearance, with tall columnar mucous cells lining and filling the alveoli and gradually producing a slow, malignant downhill course. No definite carcinoma cells were seen in the cytologic smear. Since this is a peripheral process, bronchoscopic examination would, of course, be negative. This tumor rarely metastasizes; a few have spread to regional lymph nodes. It gradually obliterates the air spaces of the lung, causing severe dyspnea and cyanosis often out of proportion to the x-ray changes. Watery or tenacious mucoid sputum secreted by these mucoid cells in profuse amounts is characteristic, often amounting to one or two pints a day, and I think that is the single most valuable diagnostic sign. I am puzzled by the yellow sputum. I suppose that there was some secondary bronchopneumonia. I am also puzzled by the one large hemorrhage described. Bleeding is not a common feature of pulmonary adenomatosis and, when it occurs, is usually slight. Usually, there is not much fever associated with pulmonary adenomatosis; if there is fever, it is low grade. I think this man had a low-grade fever considering the extent and severity of the disease. The course is usually chronic, progressive and downhill; the disease in all the case reports that I have read has been fatal after a long period of dyspnea, productive cough, cyanosis and profound weakness. Usually, surgical removal is not satisfactory because the disease often originates in various parts of both lungs and continues to spread after operation. I think pulmonary adenomatosis is the most likely primary disease here, whether or not it was actually restricted to one lobe. I think the patient undoubtedly had coronary-artery disease, probably an old coronary thrombosis and a small cerebral embolus or thrombosis.

Dr. Helen S. Pittman: I saw this man regularly. Our diagnosis was alveolar-cell carcinoma during the early months of his illness, but I later abandoned it when the lesion remained stationary for so long. He was desperately short of breath and very sick and presented difficult problems both of diagnosis and of management.

A Physician: Why may this not have been bronchiectasis?

Dr. Pier: I suppose it could have been. He had no clubbing, and apparently the laminograms did not show a great deal of bronchiectasis. It was upper-lobe disease without evidence of tuberculosis, and I am particularly impressed by the mucoid sputum.

Dr. Hanelin: It would be most unusual to have this extensive bronchiectasis without considerable collapse of the lung; that is almost invariable.

Dr. Lewis Kane: How often have you seen cases with adenomatosis confined to one lobe of one lung?

Dr. Hanelin: Personally, I have not, but Dr. Robbins has seen one or two cases in which the disease has been confined to one lobe at the time of surgery.

Clinical Diagnosis

Chronic nontuberculous pneumonitis.
?Alveolar-cell carcinoma.

Dr. Arthur S. Pier's Diagnoses

Adenomatosis of lung.
Coronary-artery disease.
Cerebral embolism or thrombosis.

Anatomical Diagnosis

Pulmonary adenomatosis.

Pathological Discussion

Dr. F. Thomas Gephart: At operation the lung was unusual; there were vascular adhesions of the superior portion of the upper lobe, and the entire upper lobe except for a portion of the lingula was quite firm and had the consistence of liver, adding to the technical difficulty of resection. The patient had an excellent anesthesia however, went through the operation very well and has done well since. The arterial oxygen saturation was 87 per cent before and 97 per cent after operation. The patient gradually improved and left the hospital after about

twelve days only to come back with acute pancreatitis. This improved rapidly, and he has now been discharged from the hospital. There were no other foci of tumor that we could find in the left lung.

Dr. Edgar B. Taft: I think Dr. Pier is to be congratulated for making the diagnosis of pulmonary adenomatosis in this case. We routinely fix lungs before we examine them, to preserve relations, so that this specimen was not studied extensively in the fresh state. There were a few fibrous adhesions on the surface, and the lung was grossly consolidated by tumor that appeared to be confined to the parenchyma (Fig. 2). The vast majority of the lobe except for portions of the lingula and anterior surface was occupied by firm, white tumor tissue. This was quite mucoid in appearance.

Figure 2.

Microscopically, the tumor was composed of relatively low columnar epithelium, which was lining the alveoli and respiratory ducts. Quite a few of the cells contained vacuoles that were quite consistent with mucus and there was mucus in the lumens of the alveoli and bronchioles. No hilar lymph nodes that were dissected from the specimen contained tumor. There were small scars suggesting old healed tuberculosis.

Dr. Gephart: Do you think that alveolar-cell carcinoma can be distinguished pathologically from pulmonary adenomatosis?

Dr. Taft: I am inclined to think that if a line can be drawn between the two diseases, it is pretty fine. It is probable that they are different manifestations of the same process. From the tissue we have at hand there is no evidence of a malignant lesion in the usually accepted sense — that is, of cellular anaplasia, of distant metastases outside the locally affected area or of invasion of pleura or lymph nodes. However, I do not think we can be sure that it was not alveolar-cell carcinoma without an autopsy.

Dr. Allen G. Brailey: Are these cells consistent enough to be recognized in the sputum?

Dr. Taft: That brings up one of the interesting features of the disease: the fact that it is difficult if not impossible to diagnose with certainty by ordinary means. The physicians who are most interested in the diagnosis of tumor by the smear technic believe this is one of the types that are eminently susceptible to diagnosis by such a method. This case did not yield positive smears, however. I suspect that if it had been malignant, it might have been much more likely to show positive smears, as Dr. Pier suggested. However, it is as yet impossible to assess the relative benignancy or malignancy of the tumor in this case until we have more complete knowledge of the findings in the patient as a whole. For the present we must call this a benign lesion, pulmonary adenomatosis.

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CANCER OF THE LUNG

IN a recent issue of the *British Medical Journal* Smithers,[1] radiotherapist to the Brompton Hospital for Diseases of the Chest, expresses concern about the "alarm" that may be created among the general public by undue publicity accorded to recent statistical research on carcinoma of the lung. That Smithers is not alone in his concern is evident from recent correspondence[2,3] in the same journal that followed the comprehensive study of Doll and Hill[4] earlier in the year. Smithers contends, and these are also the basic arguments of other correspondents, that, although one can guess at the nature of some of the factors responsible for the increasing frequency with which cancer of the lung is given as the primary cause of death, the relative importance of each of these factors is not known — especially since the evidence linking cigarette smoking and lung cancer is incomplete. The medical profession, should therefore "beware of putting extravagant accounts of rising cancer death rates and their causes before the public."

Are these accounts extravagant? Smithers places stress on the lack of knowledge of the extent of the true increase in lung cancer. At the same time, he states that the recorded increase is due in large part to changing age distribution of the population and improved diagnosis, with the implication that the true rise in incidence has been comparatively small. In view of lack of knowledge needed to settle the point, speculation in either direction is indecisive, but many competent people consider the reverse situation to be much more probable — that the startling rise in lung cancer during the past few decades is real. They compare the increase in carcinoma of the lung with that of other internal sites — for example, the large intestine — and point out the disparity in the percentage increases (133 and 3.5, respectively, between 1940 and 1950).[5] In addition, they question whether diagnostic measures have improved to anything like the degree necessary to account for an increase of 133 per cent between 1940 and 1950. However, this trend is a secondary consideration, since it forms no part of the evidence incriminating tobacco as an etiologic factor. In the United States and in Great Britain lung cancer accounts for between a twentieth and a thirtieth of all deaths in men of middle age. Consideration of present incidence and death rates, quite apart from past experience, is sufficient to justify concern.

Whether undue concern has been or is being raised among the general public is to be questioned. The latest study of Doll and Hill,[4] based on 1465 patients with cancer of the lung and 1465 matched controls, was carefully conducted and yielded evidence of an association between cigarette smoking and lung cancer so strong as to be considered proof within the everyday meaning of the word. Even before presentation of this work, evidence in favor of such an association was strong, deriving especially from a previous investigation by the same authors[6] and from an investigation of 684 cases by Wynder and Graham[7] in the United States. Male smokers

between the ages of forty-five and sixty-four experience an incidence of lung cancer between four and thirty-four times as great as that of nonsmokers of the same age, and incidence increases proportionately to the average daily consumption of cigarettes.

If such figures as these have been unduly publicized, the public, medical and lay, shows no sign of taking any of the relatively simple courses that would undoubtedly reduce the incidence of lung cancer. If similar data had incriminated a food contaminant that was not habit forming and was not supported by the advertising of a financial empire, there is little doubt that effective countermeasures would have followed quickly. It is not insufficiency of evidence that accounts for lack of such measures against tobacco tars, and it is debatable whether or not a little more "alarm" would be amiss. It is true that the causative mechanism underlying the association between tobacco and lung cancer is not known, although there is ample room for speculation in the presence of known carcinogens in tobacco tar; also, little is known about dosage, filtration of smoke and other factors that bear on the subject. However, if control of cholera had not been initiated empirically, but had awaited demonstration of the vibrio, active and useful preventive measures would have been delayed fifty years.

The situation affords unusual opportunities for the vast tobacco interests to support impartial researches into the effects that their products may have on human health.

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MINNESOTA CENTENARY

THE hundredth anniversary of the Minnesota State Medical Association was celebrated last May at an annual meeting attended by more than 4000 physicians and guests. The program included addresses (all of which are published in the August issue of *Minnesota Medicine*) by Dr. Richard Trail, of London, head of the Papworth and Enham–Alamein rehabilitation centers for tuberculous patients, Sir Alexander Fleming, director of St. Mary's Wright Fleming Institute of London, and Dr. Alton Ochsner, chairman of the Department of Surgery at Tulane University of Louisiana School of Medicine. Not the least interesting feature of the meeting was the exhibition of a typical doctor's office of a hundred years ago.

Medical advances in Minnesota in the period marked by this anniversary are all the more impressive when considered against the background of the evolution of Minnesota from a territory to a state. Ten years before the organization of the Minnesota State Medical Association on July 23, 1853, there was only one civilian doctor west of Prairie du Chien. Today, the names of the State's leaders in medical and surgical research and practice are bywords in the rest of the nation and throughout the world.

Confident that the next century will more than match the notable progress of the last, the *Journal* congratulates the Minnesota State Medical Association on an anniversary extraordinarily full of meaning to all concerned with the advancement of medical science.

MEDICAL REHABILITATION

THE Bay State Medical Rehabilitation Clinic, put in operation at the Massachusetts General Hospital in June, 1951, has presented the accounting of its first two years of service. During this period its patient-treatment visits have increased from 3153 in the first year to 5363 in the second, a total of 448 patients having been admitted.

The disposition of this group has been broken down into 114 patients with degenerative and 110 with traumatic conditions discharged, 90 still under treatment, 74 who were referred for evaluation only, and 60 who discontinued attendance for one reason or another. In the degenerative cases 38 patients were returned to work and the rest aided in other ways, such as the institution of a home program or referral elsewhere, and in the traumatic cases 62 patients were returned to gainful employment and the remaining 48 otherwise aided.

Clinic referrals have come from all the New England states and beyond, many of them from coal-mining areas through arrangements with the United Mine Workers Welfare and Retirement Fund. Operating at a financial loss so far as its earned income is concerned, the Clinic has remained solvent through the enlightened generosity of the Bay State Society for the Crippled and Handicapped.

The directors, corporation and staff of the Clinic have every right to be pleased with these two years of increasing success; an area noted for its good works is to be congratulated on such an addition to its list of social agencies.

POSTGRADUATE MEDICAL INSTITUTE, 1953-1954

THE notable and encouraging success of the Postgraduate Medical Institute in its first year promises to be matched in the ensuing sessions, the program of which appears elsewhere in this issue of the *Journal*. Sponsored by the Massachusetts Medical Society and other agencies concerned with medical education, the Institute has not only acted as a clearing house of medical information but also conducted postgraduate teaching courses for physicians. The schedule for 1953-1954 is made up of weekly sessions in Boston (October 7 to April 14), Fitchburg (November 18 to March 17), New Bedford (October 7 to December 23) and Springfield (October 16 to December 18). A monthly seminar, beginning in October, will be held in Gardner, and weekly courses in Framingham, Fall River and the Berkshire area are planned.

The subjects of the sessions will include most phases of medical, surgical and public-health practice. Of particular interest are the television programs on cancer, to be presented in the Jimmy Fund Auditorium, Children's Medical Center, Boston. The first six programs, starting on October 21, will be biweekly and will be followed by weekly programs on Wednesdays.

The impressive schedule announced by the Institute cannot fail to interest physicians who desire to keep abreast of the rapid advances in general medicine and the specialties. The Institute deserves the highest commendation for its efforts to improve medical practice by means of postgraduate courses in the principal centers of Massachusetts.

A man wrote to his physician that having taken cold, he "got a little horse," and asked what he should do. The doctor recommended a saddle and bridle.

Boston M. & S. J., *September 14, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

SIMMONS — Channing C. Simmons, M.D., of Boston, died on August 15. He was in his seventy-seventh year.

Dr. Simmons received his degree from Harvard Medical School in 1899. He was formerly consulting surgeon, Massachusetts General Hospital, assistant director, State Department of Public Health, Division of Cancer, and was serving as consultant to the committee on hospitals for the Governor of Massachusetts.

He was a member of the American Surgical Association, the New England Surgical Society, the American Cancer Society, the New England Cancer Society, the Boston Surgical Society and was a fellow of the American College of Surgeons and of the American Medical Association.

There are no survivors.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1953

RÉSUMÉ

DISEASE	JULY 1953	JULY 1952	SEVEN-YEAR MEDIAN
Chancroid	6	1	2
Chicken pox	439	419	490
Diphtheria	2	0	14
Dog bite	1450	1404	1382
Dysentery, bacillary	92	0	9
Encephalitis, infectious	1	2	2
German measles	124	557	121
Gonorrhea	170	125	257
Granuloma inguinale	0	0	0
Hepatitis, infectious	73	11	4†
Lymphogranuloma venereum	0	0	0
Malaria	6	12	12
Measles	102	611	1162
Meningitis, meningococcal	3	4	5
Meningitis, Pfeiffer bacillus	3	6	2
Meningitis, pneumococcal	2	2	2
Meningitis, staphylococcal	1	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	2	3	4
Mumps	614	233	383
Poliomyelitis	69	30	21
Salmonellosis	25	12	7
Scarlet fever	71*	46	120
Syphilis	197	173	173
Trichinosis	5	3	2
Tuberculosis, pulmonary	255	221	227
Tuberculosis, other forms	14	15	13
Typhoid fever	0	1	3
Undulant fever	3	3	4
Whooping cough	126	107	387

*Includes streptococcal sore throat.
†Four-year median.

COMMENT

Diseases below the seven-year median included chicken pox, diphtheria, measles, scarlet fever and whooping cough.

Two cases of diphtheria were reported in July. This brings the total number of cases for the fourteen consecutive months since June 1, 1952, to only 19.

The 102 cases of measles reported make this the lowest figure, by a considerable margin, for the month of July.

Diseases above the seven-year median were bacillary dysentery, infectious hepatitis (four-year median), mumps, poliomyelitis and salmonellosis.

Some of the enteric diseases — namely, bacillary dysentery, infectious hepatitis and salmonellosis — showed marked increases during the month of July as compared with the same month in recent years. The increase in the number of reported cases of infectious hepatitis can be attributed primarily to more complete reporting, but the increases in the number of reported cases of the other two diseases are due in large part to small localized outbreaks and family outbreaks in which person-to-person contact is the principal avenue of spread.

Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Boston, 1; Chicopee, 1; total, 2.

Dysentery, bacillary: Auburn, 1; Beverly, 1; Boston, 32; Brockton, 4; Danvers, 10; Fitchburg, 1; Greenfield, 1; Lowell, 1; Lynn, 1; Newton, 1; Quincy, 1; Salem, 5; Shelburne, 2; Shrewsbury, 1; Tewksbury, 2; Wellesley, 1; Woburn, 1; Worcester, 26; total, 92.

Encephalitis, infectious: Weymouth, 1.

Hepatitis, infectious: Belchertown, 9; Belmont, 2; Boston, 10; Bourne, 1; Cambridge, 2; Charlton, 2; Chelsea, 1; Falmouth, 1; Fort Devens, 2; Grafton, 1; Lynn, 1; Manchester, 1; Methuen, 4; Milford, 1; Millbury, 3; Newton, 2; Palmer, 4; Peabody, 1; Pittsfield, 2; Quincy, 1; Scituate, 1; Sharon, 2; Somerset, 1; Somerville, 1; Springfield, 1; Sutton, 1; Waltham, 2; Worcester, 13; total, 73.

Malaria: Cambridge, 1; Fort Devens, 2; Murphy Army Hospital, 2; Saugus, 1; total, 6.

Meningitis, meningococcal: Holbrook, 1; Lawrence, 1; Salem, 1; total, 3.

Meningitis, Pfeiffer bacillus: Haverhill, 1; Lawrence, 1; Middleboro, 1; total, 3.

Meningitis, pneumococcal: Everett, 1; Worcester, 1; total, 2.

Meningitis, staphylococcal: Medford, 1.

Meningitis, mumps: Newton, 1.

Meningitis, undetermined: Brockton, 1; Lynn, 1; total, 2.

Poliomyelitis: Agawam, 1; Barre, 1; Belmont, 1; Berlin, 1; Beverly, 1; Boston, 7; Brewster, 1; Brookline, 1; Chicopee, 1; Greenfield, 1; Hanover, 1; Holyoke, 1; Lee, 1; Leominster, 1; Lowell, 2; Medford, 1; Melrose, 1; Milton, 2; New Bedford, 1; Newburyport, 1; Newton, 2; Northbridge, 1; Norwood, 1; Peabody, 1; Plymouth, 1; Quincy, 9; Reading, 1; Scituate, 2; Springfield, 1; Taunton, 1; Townsend, 1; Walpole, 1; Warren, 1; Watertown, 1; Weston, 2; Westport, 1; Weymouth, 5; Wilmington, 1; Winthrop, 1; Worcester, 7; total, 69.

Rocky Mountain spotted fever: Scituate, 1.

Salmonellosis: Attleboro, 1; Belmont, 1; Boston, 5; Brockton, 2; Cambridge, 1; Chelmsford, 1; Chicopee, 1; Lowell, 1; Marblehead, 1; Salem, 1; Scituate, 1; Springfield, 4; Taunton, 1; Waltham, 1; Watertown, 1; Winthrop, 1; Worcester, 1; total, 25.

Trichinosis: Cambridge, 1; Medford, 1; North Andover, 3; total, 5.

Undulant fever: Beverly, 1; Newton, 1; West Stockbridge, 1; total, 3.

CORRESPONDENCE

CORRECTION OF UNWARRANTED STATEMENT

To the Editor: Like many other privately endowed medical institutions, the Albany Medical College, as the nucleus of an ever-improving and expanding Albany Medical Center, has been and is struggling to overcome severe financial obstacles to its growth and expansion during the last decade. In this effort we have counted heavily on the understanding, the services and the financial support of the physicians of the fourteen counties of our Medical Center orbit. This support has been attained in fair measure but only after diligent efforts on the part of the loyal faculty members, who have patiently spread the word regarding the services that the Medical Center has to offer. It is to be feared that much of this good work may be undone by a single loose and undocumented statement in the correspondence, "Regarding the Rip Van Winkle Clinic," in the July 30 issue of the *Journal*. Great harm has already been done by the implication that the dean of the Albany Medical College is in the habit of telling his former students not to practice in a certain area. The reflection against me as a person is hardly serious, but as the official administrator of the institution it is extremely serious and requires immediate refutation in your correspondence column.

For the sake of brevity, permit me to say that in the incident mentioned I made no attempt whatsoever to discourage or to encourage the young physician's decision to practice medicine in Germantown, New York. This was made known to some of the authors of the correspondence referred to long before it was written for publication.

Since that letter and, hence, the statement may be read and misinterpreted by many physician friends of the Albany Medical College in other areas, and since it is imperative that the integrity and judgment of its administrative officer be not readily jeopardized by such an irresponsible and unethical statement by a group of Columbia County physicians, I request your immediate cooperation in urging the publication of this letter in toto in the correspondence column of your next issue.

Harold C. Wiggers, Ph.D.
Dean
Albany, New York — Albany Medical College

BOOK REVIEWS

Synovial Fluid Changes in Joint Disease. By Marian W. Ropes, M.D., and Walter Bauer, M.D. 8°, cloth, 150 pp., with 15 illustrations and 14 tables. Cambridge: Harvard University Press, 1953. $4.00.

There has long been a need for tables of values for the constituents of normal synovial fluid. Such tables are provided in this book, which represents the results of investigations on synovial fluid for the past twenty years. The authors believe that synovial fluid is a dialysate of blood plasma to which mucin, secreted by the synovial tissue cells, has been added. Pathologic synovial fluids can be divided into two groups, the first representing inflammatory reactions of traumatic origin, including degenerative joint disease and neuroarthropathy, and the second the synovial fluids of all types of infectious arthritis, including Reiter's syndrome and rheumatoid arthritis.

Most of the aspirations of articular fluid were obtained from the knee joint. There are numerous tables of the cytology, chemistry and characteristics of the mucin. A high concentration of protein and especially globulin usually indicated an inflammatory reaction, not traumatic in origin. The protein content rose with longer duration or increased severity of the disease. Normal synovial fluid contained no fibrinogen.

The concentration of mucin is also related to the type, severity and duration of the articular disease. The sugar concentration is of diagnostic value and is usually lower in infectious arthritis. A white-cell count above 5000 per cubic millimeter or an absolute count of polymorphonuclear leukocytes above 500 per cubic millimeter is probably not traumatic in origin. There is little change from the normal values in synovial fluids in traumatic cases. The electrolytes and protein are only a little higher than normal with normal values for mucin and sugar. Tumors in or about the joint tend to show the characteristics of fluids typical of traumatic changes. In the fluids in infectious cases the sugar is lower but with wide variations, with a high content of mucin and protein. The nucleated cell count is usually above 3000, with more than 500 polymorphonuclear leukocytes.

The authors show that synovial fluid is a reflection of inflammation of the tissues and can be of help in diagnosis of articular diseases. This book should be of value to all students of articular disease.

John G. Kuhns, M.D.

Prescription for Rebellion. By Robert Lindner. 8°, cloth, 305 pp. New York: Rinehart and Company, Incorporated, 1952. $3.50.

The world is sick today, and the individuals within are afflicted with the greatest scourge of history — the forces of adjustment. What makes the situation even more critical is the fact that sociologists, scientists, politicians, artists and religious leaders are all advocating adjustment, and while the leaders in the fields of psychology and psychiatry, to whom the rest are turning for guidance, are likewise riding the adjustment trail, and chasing all deviants from the straight and narrow back into the fold. With excellent delineation and magnificent vocabulary,

this volume presents a new concept of the basic ills affecting man and society, emphasizing the conflict with the instinct of rebellion versus adjustment. This psychologic instinct is "unique to Man, and gives him the power to manipulate and control his environment" and at the same time "compensates for his biological weakness, for his helplessness at birth." No one would dispute that this is the Age of Anxiety, but how many would consider that anxiety can arise from the attempts of the patient to adjust himself? In attempting to assuage anxiety in one form, a new anxiety may be created. Most present-day psychotherapeutic approaches merely substitute the neurosis of "conformity, surrender, passivity, social apathy and compliance" for the original complaint, and the somatic therapies and psychosurgical approaches are often a grosser exaggeration of this substitution.

The author takes great pains to clarify what he means by "instinct" and "rebellion" and points out that these terms by common usage are accepted as negative qualities, and in some respects immoral, whereas he, of course, regards them as being highly positive and creative. He assumes that everyone is aware of the meaning of adjustment, but it is on this very point that the author is most vulnerable. Throughout the volume he intermixes conformity and adjustment, and gives a purely negative connotation to the terms as may be noted in the partial quotation given above. It appears to the reviewer that many a nonconformist could comfortably sit at the court of adjustment, and what the author is really attacking is the passive, subdued, ineffectual conformist, who has lost his individuality and his creativeness. That this is so is seen in the last third of the book, where the prescription for rebellion is outlined and the rebel is encouraged to develop a sense of awareness, a sense of self and an attitude of skepticism. The sense of awareness means insight into one's motivating forces and the ability to increase the range of cortical control so that worthy aims are attained instead of the rebel's becoming a crippled slave of the unconscious. It is also interesting that the author considers tension as a prerequisite, implying a state of restlessness associated with dissatisfaction of the status quo and having the desire to effect changes.

The many excellent features of this book, including a diverting psychologic study of history, are weakened in the reviewer's opinion when the author tends to elevate his own position by critically reducing the status of some of the giants of the field while frequently borrowing from their most fertile contributions. Similarly, many contemporary colleagues are not going to enjoy his sweeping derogations of their sincere, though perhaps misguided, efforts. This is a pity, for the presentation should command the attention of all in the field, and it will serve to awaken many of the "adjusting" school from their smug complacency. Lindner writes remarkably forcibly, and has the ability to make his words almost jump off the page. In this age, in which there is a plethora of mumbo-jumbo and confusion in psychologic texts, it is refreshing to find a book in which the meaning is always clear. In addition to the main theme, there are many interesting asides, all of which add to the picture of the author's being very well informed and erudite. The inclusion of an index would have increased the value of the volume.

IAN HAY BROWN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Body Temperature: Its changes with environment, disease and therapy. By W. A. Selle, Ph.D., professor of biophysics and physiology, University of California School of Medicine, Los Angeles. 8°, paper, 112 pp., with 23 charts. Springfield, Illinois: Charles C Thomas, 1952. $3.50. (Publication No. 147, *American Lecture Series.*)

In this small monograph Dr. Selle gives an outline of body temperature and its regulation. There is a special chapter on physical allergy, the sensitivity to heat or cold. The literature of the subject is discussed, and there is a bibliography of 222 references. The book should be in the reference collections of all medical libraries.

Transactions of the Tenth Scandinavian Congress of Pathology and Bacteriology, in Bergen, June 16th–18th, 1952. Under the chairmanship of Th. M. Vogelsang, M.D.; secretary general of the Congress, Per Oeding, M.D. 8°, paper, 435 pp., with illustrations. Copenhagen: Ejnar Munksgaard, 1952. (*Acta Pathologica et Microbiologica Scandinavica*, Supplementum XCIII.)

This volume contains the large number of papers read at the Congress. There are indexes of authors and subjects.

Treatment of Respiratory Emergencies Including Bulbar Poliomyelitis. By Thomas C. Galloway, M.D. 8°, paper, 94 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1953. $3.00. (Publication No. 168, *American Lecture Series.*)

Most of this small monograph deals with acute bulbar poliomyelitis and its treatment. There is a chapter on tracheotomy in other diseases with respiratory obstruction. There is a bibliography of 115 references.

Chemical Induction of Cancer. By George Wolf, D.Phil., assistant professor, University of Illinois. 12°, cloth, 250 pp., with illustrations. Cambridge: Harvard University Press, 1952. $3.50.

Dr. Wolf has evaluated the present knowledge of the experimental induction of tumors by chemical agents. The first five chapters consist of a discussion of the subject in general. The remainder are devoted to carcinogenic hydrocarbons, azo compounds and carcinogenic aromatic acids and derivatives. Lists of selected references are appended to the chapters. The book should be in all collections on the subject.

Disabilities and How to Live with Them. By 55 patients. 8°, cloth, 243 pp., with 4 illustrations. London: The Lancet Limited, 1952. 10s. 6d.

This monograph presents a collection of letters written to the *Lancet* by patients or former patients describing their experiences in overcoming disabilities of various types. The small book is a distinct contribution to medical sociology.

The Pharynx: Basic aspects and clinical problems. Edited by Abraham R. Hollender, M.D., attending otolaryngologist and chairman of the service, Mount Sinai Hospital of Greater Miami, and consulting otolaryngologist, Variety Children's and St. Francis hospitals, Miami Beach, Florida. 8°, cloth, 560 pp., with 28 illustrations. Chicago: Year Book Publishers, Incorporated, 1953. $15.00.

This special monograph is the joint work of 20 contributors. The text is divided into two main sections. The first deals with basic aspects. The second is divided into five parts, on the nasopharynx (epipharynx), mouth and pharynx (oropharynx), the uvula, salivary glands and neck, tuberculosis, syphilis, neoplasms and miscellaneous considerations. There are 31 chapters, and bibliographies are appended to all of them. There is a good index, and the book is well published. It should be in all medical libraries.

Congenital Anomalies of the Heart and Great Vessels. By Maurice A. Schnitker, M.D., director of medicine, St. Vincent's Hospital, senior member, active staff, Toledo and Maumee Valley hospitals, and member, consulting staff, St. Luke's and Toledo State hospitals. 8°, cloth, 306 pp., with 19 illustrations. New York: Oxford University Press, 1952. $8.00.

This monograph discusses and evaluates the important literature on congenital anomalies of the heart and great vessels. The first five chapters deal with embryology and morphology, etiology, incidence and associated phenomena. Then, in order, acyanotic lesions, the cyanose-tardive group, the cyanotic group (morbus caeruleus) and complicating conditions are discussed. Bibliographies are appended to the various anomalies; there is a good index, and the publishing is excellent. The book should be in all collections on cardiovascular disease.

A Vitamin Digest. By Guy W. Clark, technical director, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. 8°, cloth, 254 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $6.50.

Dr. Clark, in this special book, discusses the development of the vitamins and their uses during the past forty years. Each of the known vitamins is considered at length, and bibliographies are appended to the various chapters. There is a good index, and the monograph is well published. It should be in the reference collections of all medical libraries.

Physical Examination of the Surgical Patient. By J. Englebert Dunphy, M.D., associate clinical professor of surgery, Harvard Medical School, surgeon, Peter Bent Brigham Hospital, and consultant in surgery, Children's Medical Center; and Thomas W. Botsford, M.D., clinical associate in surgery, Harvard Medical School, senior associate in surgery, Peter Bent Brigham Hospital, and associate in surgery, Children's Medical Center. 8°, cloth, 326 pp., with 188 illustrations. Philadelphia: W. B. Saunders Company, 1953. $7.50.

NOTICES

ANNOUNCEMENT

Dr. Maurice R. Ruben announces the removal of his office from 311 Commonwealth Avenue, Boston, and 570 Blue Hill Avenue, Roxbury, to 151 Maple Street, Springfield, Massachusetts, in association with Dr. Gerald I. Lichter for the practice of ophthalmology and otolaryngology.

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The fall clinical assembly of the Massachusetts Academy of General Practice will be held in Boston on September 23. The program is as follows:

9:30 a.m. to 12:00 m. New England Deaconess Hospital — Dr. Elliot P. Joslin, chairman.

12:00 m. to 1:00 p.m. Registration (Bay State Room, Hotel Statler), followed by buffet luncheon.

2:00 p.m. Lecture.

3:15 p.m. Cardiac surgery symposium. Dr. Gordon S. Myers, chairman.

4:30 p.m. Business meeting.

5:45 p.m. Cocktail hour and dancing.

7:30 p.m. Dinner.

MEDICAL AND DENTAL MILITARY SYMPOSIUM

The third medical and dental military symposium will be held at the United States Naval Hospital, Chelsea, October 12 through 14. Civilian physicians and dentists and members of allied sciences are invited to attend.

The Chief of Naval Personnel has approved the symposium for retirement point credit for those Reservists not on the Inactive Status List. One retirement point credit will be awarded for each of the three sessions attended, provided the duration of the meeting is at least two hours. Appropriate duty orders are authorized for those who request them. Requests for orders should be submitted to the Commandant of the First Naval District. A representative of the District Medical Office, First Naval District, will be present to record the names of those attending.

ESSEX NORTH DISTRICT MEDICAL SOCIETY

The next meeting of the Essex North District Medical Society will be held Wednesday evening, September 30, at the Amesbury Country Club, Amesbury, at 6:45 p.m. Dr. Charles G. Hayden will speak on the subject "Current Thinking in Regard to Expansion of the Blue Cross-Blue Shield Program."

AMERICAN CANCER SOCIETY CLINICAL FELLOWSHIPS AND TRAINEESHIPS

Clinical fellowships or traineeships of the American Cancer Society will be made available to hospitals offering postgraduate training (residencies and fellowships) in cancer, surgery, specified surgical specialties (obstetrics and gynecology, orthopedic surgery, otolaryngology and urology), radiology, pathology and internal medicine, and approved for such training by the Council on Education and Hospitals of the American Medical Association. Emphasis must be placed on the diagnosis and treatment of cancer in the training program of the hospitals.

Applicants must be graduates of Class A medical schools in the United States, its territories or Canada, not over forty years of age on the birthday after the beginning of the training and citizens of the United States, and must conform in other respects to the requirements of the institution to which application is made. Clinical fellowships will be awarded to physicians who have completed a year of postgraduate training, in addition to internship, for certification by the appropriate medical specialty board in one of the specialties listed above; applicants for clinical traineeships must have completed a full year's internship. Stipends will be $3600 a year for fellowships and less than that amount (commensurate with the level of training) for traineeships.

Applications from institutions must be filed with the director, Professional Education Section, American Cancer Society, 47 Beaver Street, New York 4, New York, before October 5, 1953. No forms are necessary, but letters of application should include the following information: number of fellowships and traineeships applied for; funds available from other sources for partial support of fellows and trainees; name of person who will supervise the training of the fellow or trainee and to whom he will be directly responsible; date fellowship or traineeship will begin; and a thorough documentation of the training that will be received at the institution, including facilities available (such as tumor clinics and opportunities for diagnosis, treatment and clinical research).

Physicians desiring such fellowships or traineeships should consult the appropriate authority in the institution of their choice.

NEW YORK DIABETES ASSOCIATION

The "First Symposium Day on Diabetes" of the New York Diabetes Association will be held on Thursday, October 8, at the Memorial Center for Cancer and Allied Diseases, New York City. Authoritative summaries and reviews of current research in the field of diabetes and general metabolism with application to the practice of medicine will be presented at morning and afternoon sessions.

A dinner program will follow in the evening. J. S. L. Browne, Ph.D., M.D., director, University Clinic, Royal Victoria Hospital, Montreal, Canada, will speak on the subject "Certain Concepts and Difficulties in Clinical Endocrinology."

Physicians, medical students and other professional personnel are invited to attend. However, because of limited seating capacity, advance registration is necessary.

PHI DELTA EPSILON ANNUAL LECTURE

Dr. Nicholas J. Eastman will deliver the annual lecture of the Beta Zeta chapter of Phi Delta Epsilon Fraternity, Hahnemann Medical College, on October 2, at 8:30 p.m., in the Klahr Auditorium, Hahnemann Medical College, 235 North Fifteenth Street, Philadelphia. The subject of the lecture will be "Twenty-Five Years of Obstetrical Pain Relief: What have we learned?"

All interested persons are cordially invited.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 15. South End Medical Club. Page 344, issue of August 20.

SEPTEMBER 17. New England Pathological Society. Page 428, issue of September 3.

SEPTEMBER 23. Middlesex South District Medical Society. Page 260, issue of August 6.

SEPTEMBER 23. American Medical Writers' Association. Page 386, issue of August 27.

SEPTEMBER 23. Massachusetts Academy of General Practice. Fall Clinical Assembly. Notice above.

SEPTEMBER 23–25. Mississippi Valley Medical Society. Page 386, issue of August 27.

SEPTEMBER 24–OCTOBER 1. Fourth Congress of Pan American Medical Women's Alliance. Page 124, issue of July 16.

SEPTEMBER 30. New England Pediatric Society.

SEPTEMBER 30. Essex North District Medical Society. Notice above.

OCTOBER 2. Phi Delta Annual Lecture. Notice above.

OCTOBER 4–9. American Academy of Pediatrics. Pages 1126, issue of June 25.

OCTOBER 5–DECEMBER 7. Postgraduate Seminar in Neurology and Psychiatry. Page 428, issue of September 3.

OCTOBER 5–DECEMBER 21. Hartford Medical Society Program. Page 260, issue of August 6.

OCTOBER 7–DECEMBER 2. Course in child psychiatry (pediatric neuropsychiatry). Page 428, issue of September 3.

OCTOBER 8. New York Diabetes Association. Notice above.

OCTOBER 12–14. National Gastroenterological Association. Page 260, issue of August 6.

OCTOBER 12–14. Medical and Dental Military Symposium. Notice above.

(Notices concluded on page xvii)

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MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

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MIDDLESEX WEST

OCTOBER 14, 1953 — MAY 12, 1954
Wednesdays monthly, 6 sessions 8:15-10 p.m.; 2 sessions 1-3 p.m. (Total 15 hours)
MARLBORO, FRAMINGHAM UNION, LEONARD MORSE AND MILFORD HOSPITALS
Fee $25

FALL RIVER

OCTOBER 7 — NOVEMBER 18, 1953 AND MARCH 10 — APRIL 14, 1954,
Wednesdays 11 a.m.–2 p.m. (Total 30 hours)
ST. ANNE'S, TRUESDALE AND UNION HOSPITALS, Fall River
Fee $30 (entire course); **$20** (spring or fall session)

NEW BEDFORD

OCTOBER 7 — DECEMBER 23, 1953
Wednesdays 2-4 p.m. (Total 20 hours)
ST. LUKE'S HOSPITAL, New Bedford
Fee $30

BERKSHIRE COUNTY

OCTOBER 7 — DECEMBER 23, 1953
Wednesdays 4-6 p.m. (Total 20 hours)
ST. LUKE'S HOSPITAL, Pittsfield
Fee $30

FITCHBURG

NOVEMBER 18,* DECEMBER 9, 1953, JANUARY 6, FEBRUARY 10 AND MARCH 17, 1954
Wednesdays 2–5 p.m. (Total 17 hours)
THE BURBANK HOSPITAL, Fitchburg
Fee $25
*All-day session

WESTERN MASSACHUSETTS

OCTOBER 16 — DECEMBER 18, 1953
Fridays 7-9 p.m. (Total 20 hours)
HOLYOKE SOLDIERS' HOME, Holyoke
Fee $25

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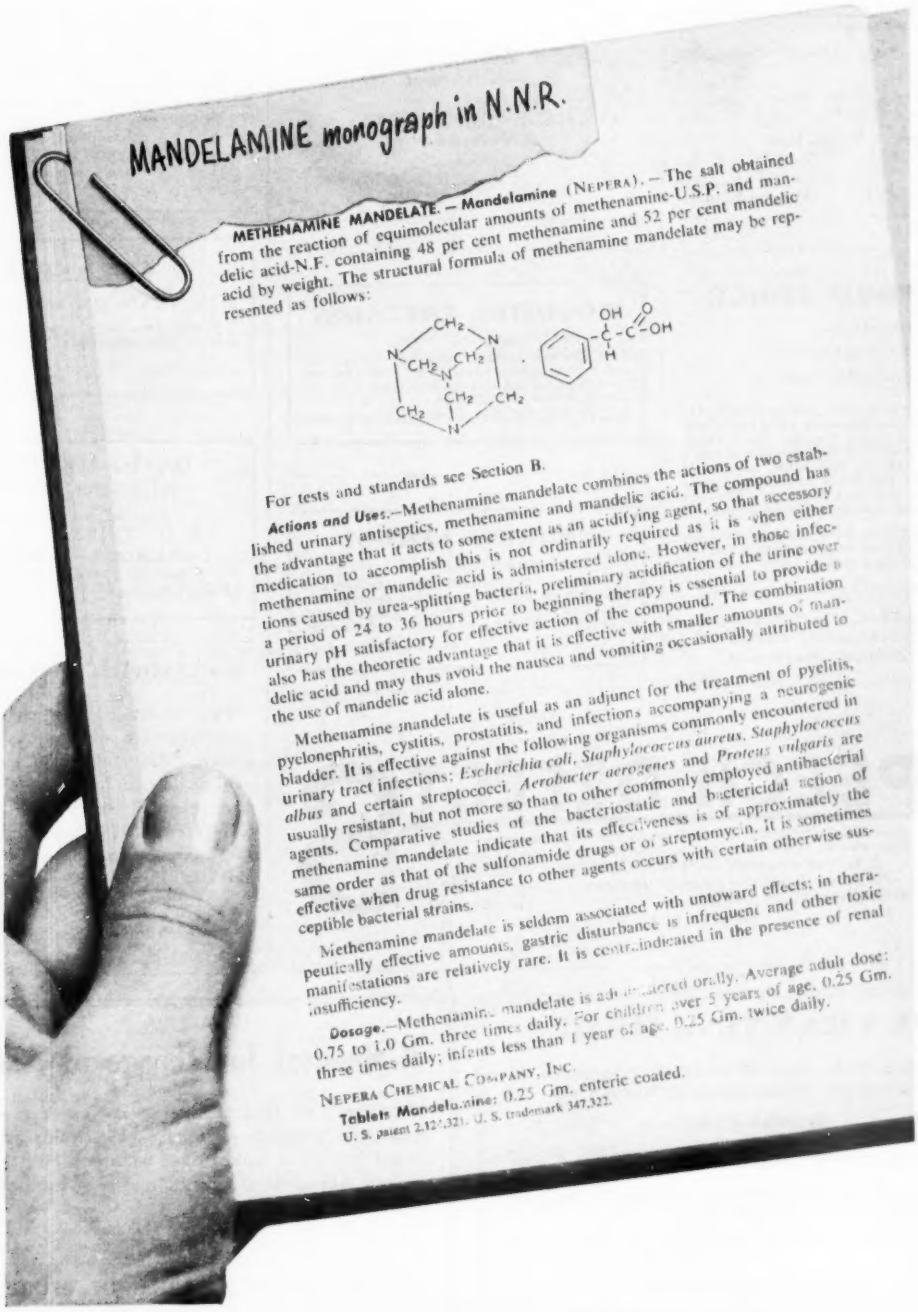
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NOTICES (*Concluded from page 470*)

OCTOBER 12–17. Seventh International Congress of Pediatrics. Page 170, issue of July 23.

OCTOBER 15–17. Annual Course in Postgraduate Gastroenterology. Page 260, issue of August 6.

OCTOBER 16. New England Society of Anesthesiologists. Page 428, issue of September 3.

OCTOBER 17–20. American Association of Blood Banks. Page 1126, issue of June 25.

OCTOBER 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

OCTOBER 25–29. American Institute of Dental Medicine. Page 124, issue of July 16.

OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

NOVEMBER 2–4. New England Postgraduate Assembly. Hotel Statler, Boston.

NOVEMBER 19 and 20. Inter-Society Cytology Council. Page 170, issue of July 23.

DECEMBER 6. American Academy of Dental Medicine. Page 170, issue of July 23.

MAY 31–JUNE 3, 1954. American Urological Association. Page xvii, issue of July 23.

SEPTEMBER 12–15, 1954. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18, 1954. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

SEPTEMBER 30. Amesbury Country Club, Amesbury. 6:45 p.m.

MIDDLESEX EAST

SEPTEMBER 23.
NOVEMBER 18.
JANUARY 20. (Combined with the Auxiliary.)
MARCH 24.
MAY 12. Annual Meeting. (Harlow Dinner.)

MIDDLESEX SOUTH

SEPTEMBER 23.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 17

THURSDAY, SEPTEMBER 17

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, SEPTEMBER 18

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott P. Joslin. New England Deaconess Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, SEPTEMBER 19

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek, Stearns Auditorium, New England Center Hospital.

MONDAY, SEPTEMBER 21

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

12:00 m. Pediatric Medical Surgical Conference (Boston Floating Hospital). Pratt Lecture Hall. Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, SEPTEMBER 22

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

12:30–1:30 p.m. Medical Journal Club. Private Dining Room, New England Deaconess Hospital.

*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, SEPTEMBER 23

9:30 a.m. 7:30 p.m. Massachusetts Academy of General Practice. Fall Clinical Assembly. New England Deaconess Hospital and Hotel Statler.

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.

12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.

12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.

*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.

*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

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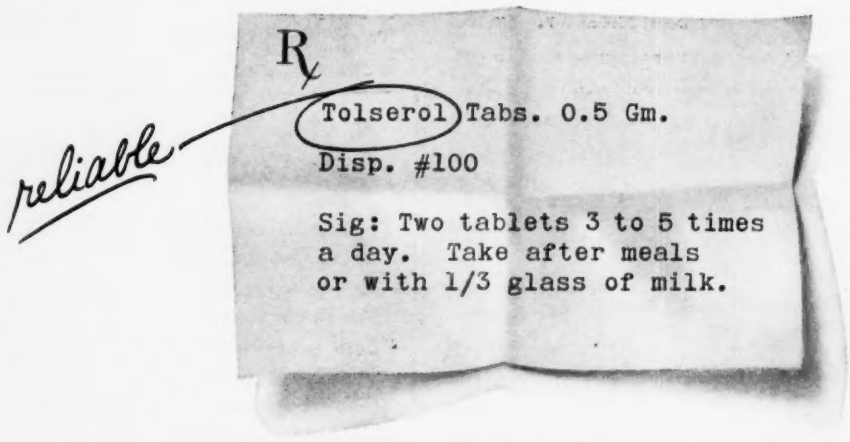

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